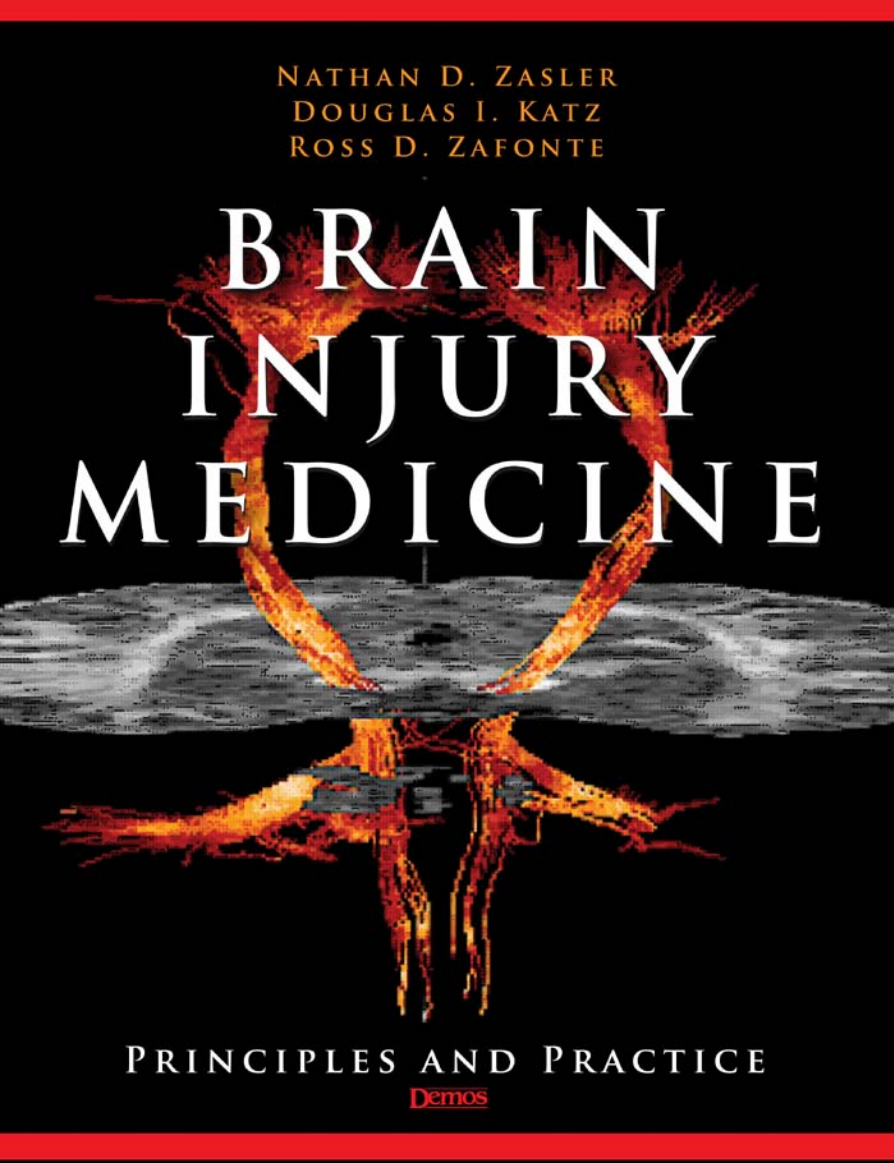


NATHAN D. ZASLER  
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# BRAIN INJURY MEDICINE

PRINCIPLES AND PRACTICE

Demos



# Brain Injury Medicine

*Principles  
and Practice*

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# Brain Injury Medicine

## *Principles and Practice*

EDITED BY

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**Demos**

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We would also like to thank the individuals at Demos Medical Publishing for their patience with this project. A special thanks to Dr. Diana Schneider for her leadership as well as her willingness to compromise. Additionally, we thank Craig Percy and Edith Barry who were essential along with other Demos staff in seeing this text come to completion.

Lastly, we would like to dedicate this book to all individuals with brain injuries, their families, and the professionals who are committed to serve and assist them in such a way as to optimize their potential to work, play, and love once again.

NZ, DK, RZ

As chief editor of this textbook, I would like to thank my co-editors, Dr. Douglas Katz of HealthSouth Brain-tree Rehabilitation Hospital and Boston University, Department of Neurology, and Dr. Ross Zafonte of University of Pittsburgh, Department of Physical Medicine and Rehabilitation, for their knowledge, patience, and expertise in assisting with the editing (and writing)

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RDZ



# Contents

<i>Preface</i>	<i>xiii</i>
<i>Foreword by Henry H. Stonnington</i>	<i>xv</i>
<i>Contributors</i>	<i>xvii</i>

## **I** PERSPECTIVES ON REHABILITATIVE CARE AND RESEARCH

1. Clinical Continuum of Care and Natural History <i>Douglas I. Katz, Nathan D. Zasler, and Ross D. Zafonte</i>	3
2. Brain Injury Rehabilitation: Past, Present, and Future? <i>George A. Zitnay</i>	15
3. International Perspectives on TBI Rehabilitation <i>Zeev Groswasser and Ofer Keren</i>	21
4. Training and Certification of Care Providers for Persons Sustaining TBI <i>Margaret A. Turk and Joanne Scandale</i>	27
5. Conducting Research in TBI: Current Concepts and Issues <i>Amy K. Wagner</i>	33

## **II** EPIDEMIOLOGY, PREVENTION, NEUROPATHOLOGY, AND NEURAL RECOVERY

6. The Epidemiology of TBI: Implications for Public Health <i>David J. Thurman, Victor Coronado, and Anbesaw Selassie</i>	45
7. Primary Prevention <i>Elena Napolitano, Jeffrey Radecki, and Elie P. Elovic</i>	57

8. TBI: Pathobiology  
*Patrick M. Kochanek, Robert S.B. Clark, and Larry W. Jenkins* 81
9. Concepts of CNS Plasticity and Their Implications for  
Understanding Recovery After Brain Damage  
*Donald G. Stein* 97
10. Advances in Innovative Therapies to Enhance Neural Recovery  
*C. Edward Dixon and Anthony E. Kline* 109

### III NEUROIMAGING AND NEURODIAGNOSTIC TESTING

11. Static Neuroimaging in the Evaluation of TBI  
*John M. Barkley, Denise Morales, L. Anne Hayman, and Pedro J. Diaz-Marchan* 129
12. Functional Neuroimaging of TBI  
*Joseph H. Ricker and Patricia M. Arenth* 149
13. Electrophysiologic Assessment Techniques:  
Evoked Potentials and Electroencephalography  
*Henry L. Lew, Eun Ha Lee, Steven S.L. Pan, and Jerry Y.P. Chiang* 157

### IV PROGNOSIS AND OUTCOME

14. Prognosis After Severe TBI: A Practical,  
Evidence-Based Approach  
*Sunil Kothari* 169
15. Neuroimaging Correlates of Functional Outcome  
*Erin D. Bigler* 201
16. Functional Assessment in TBI Rehabilitation  
*Marcel Dijkers and Brian Greenwald* 225
17. Life Expectancy  
*Robert M. Shavelle, David J. Strauss, Steven M. Day, and Kelly A. Ojdana* 247

### V ACUTE CARE

18. TBI: Pathology, Pathophysiology, Acute Care and  
Surgical Management, Critical Care Principles, and Outcomes  
*Eli M. Baron and Jack I. Jallo* 265
19. Assessment, Early Rehabilitation Intervention, and Tertiary Prevention  
*W. Jerry Mysiw, Lisa P. Fugate, and Daniel M. Clinchot* 283

## VI REHABILITATIVE CARE AND TREATMENT OF SPECIFIC POPULATIONS

20. TBI: A Pediatric Perspective  
*Andrew I. Sumich, Maureen R. Nelson, and James T. McDeavitt* 305
21. The Older Adult  
*Jeffrey Englander, David X. Cifu, and Trinh Tran* 315
22. Mild TBI  
*Grant L. Iverson, Rael T. Lange, Michael Gaetz, and Nathan D. Zasler* 333
23. Post-Concussive Disorder  
*Grant L. Iverson, Nathan D. Zasler, and Rael T. Lange* 373
24. Sport-Related Concussion  
*Michael W. Collins, Grant L. Iverson, Michael Gaetz, and Mark R. Lovell* 407
25. Assessment and Rehabilitative Management  
of Individuals with Disorders of Consciousness  
*Joseph T. Giacino, Douglas I. Katz, and Nicholas Schiff* 423

## VII NEUROLOGIC PROBLEMS

26. Post-Traumatic Seizures and Epilepsy  
*Stuart A. Yablon and Victor G. Dostrow* 443
27. Movement Disorders After TBI  
*Joachim K. Krauss and Joseph Jankovic* 469
28. Balance and Dizziness  
*Neil T. Shepard, Richard A. Clendaniel, and Michael Ruckenstein* 491
29. Evaluating and Treating Visual Dysfunction  
*William V. Padula, Lezheng Wu, Vincent Vicci, John Thomas,  
Christine Nelson, Daniel Gottlieb, Penelope Suter, Thomas Politzer, and Raquel Benabib* 511
30. Cranial Nerve Disorders  
*Flora M. Hammond and Brent E. Masel* 529
31. Fatigue: Assessment and Treatment  
*Jonathan L. Fellus and Elie P. Elovic* 545
32. Sleep Disturbances: Epidemiology, Assessment, and Treatment  
*Lora L. Thaxton and Amish R. Patel* 557
33. Diagnosis and Management of Late Intracranial  
Complications of TBI  
*David F. Long* 577

## VIII NEUROMUSCULOSKELETAL PROBLEMS

34. Complications Associated with Immobility After TBI  
*Kathleen R. Bell* 605
35. Assessing and Treating Muscle Overactivity in the  
Upper Motoneuron Syndrome  
*Nathaniel H. Mayer, Alberto Esquenazi, and Mary Ann E. Keenan* 615

## IX MEDICAL MANAGEMENT ISSUES

36. Gastrointestinal and Nutritional Issues  
*Donald F. Kirby, Linda Creasey, and Souheil G. Abou-Assi* 657
37. Sexuality, Reproduction, and Neuroendocrine Disorders  
Following TBI  
*M. Elizabeth Sandel, Richard Delmonico, and Mary Jean Kotch* 673
38. Post-Traumatic Pain Disorders: Medical Assessment and Management  
*Nathan D. Zasler, Lawrence J. Horn, Michael F. Martelli, and Keith Nicholson* 697
39. Psychological Approaches to Comprehensive Pain  
Assessment and Management Following TBI  
*Michael F. Martelli, Keith Nicholson, and Nathan D. Zasler* 723
40. Neurorehabilitation Nursing of Persons with TBI:  
From Injury to Recovery  
*Terri Antoinette* 743

## X COGNITIVE AND BEHAVIORAL PROBLEMS

41. Cognitive Rehabilitation  
*Keith D. Cicerone* 765
42. Cognitive Impairments After TBI  
*Paul J. Eslinger, Giuseppe Zappalà, Freeman Chakara, and Anna M. Barrett* 779
43. Neuropsychological Assessment and Treatment of TBI  
*Laura A. Taylor, Lee A. Livingston, and Jeffrey S. Kreutzer* 791
44. Principles of Behavioral Analysis and Modification  
*Robert L. Karol* 815
45. Neuropsychiatric Aspects of TBI  
*Thomas W. McAllister* 835

<b>XI</b>	<b>SPEECH, LANGUAGE, AND SWALLOWING PROBLEMS</b>	
46.	Assessment and Treatment of Speech and Language Disorders in TBI <i>Bruce E. Murdoch and Brooke-Mai Whelan</i>	865
47.	Evaluation and Treatment of Swallowing Problems After TBI <i>Jeri A. Logemann</i>	887
48.	Cognitive-Communication Deficits Following TBI <i>Carl A. Coelho</i>	895
<b>XII</b>	<b>MOTOR RECOVERY, FUNCTIONAL MOBILITY, AND ACTIVITIES OF DAILY LIVING</b>	
49.	Neuroscientific Basis for Occupational and Physical Therapy Interventions <i>Randolph J. Nudo and Numa Dancause</i>	913
50.	Therapy Interventions for Mobility Impairments and Motor Skill Acquisition After TBI <i>Katherine J. Sullivan</i>	929
51.	Therapy for Activities of Daily Living: Theoretical and Practical Perspectives <i>Robin McNeny</i>	947
<b>XIII</b>	<b>NEUROPSYCHOPHARMACOLOGY AND ALTERNATIVE TREATMENTS</b>	
52.	Pharmacotherapy of Neuropsychiatric Disturbances <i>Jonathan M. Silver and David B. Arciniegas</i>	963
53.	Pharmacotherapy of Cognitive Impairment <i>David B. Arciniegas and Jonathan M. Silver</i>	995
54.	Neuropharmacology: A Rehabilitation Perspective <i>Jay M. Meythaler, Ross D. Zafonte, Lisa Lombard, and Cara Camiolo Reddy</i>	1023
55.	Nutraceuticals <i>Jeffrey S. Hecht</i>	1037
56.	Traditional Chinese Medicine Theory in the Mechanism and Treatment of TBI <i>Gary G. Wang</i>	1051
57.	Complementary and Alternative Medicine <i>Jacinta McElligott, Alan M. Davis, Jeffrey S. Hecht, Sunil Kothari, John A. Muenz, Jr., and Gary G. Wang</i>	1061



## XIV PSYCHOSOCIAL AND VOCATIONAL ISSUES

58. Community Reentry Issues and Long-Term Care  
*Sally Kneipp and Allen Rubin* 1085
59. The Treatment of Substance Abuse in Persons with TBI  
*John D. Corrigan* 1105
60. A Cognitive-Behavioral Intervention for Family Members of  
Persons with TBI  
*Angelle M. Sander* 1117
61. Return to Work Following TBI  
*Michael West, Pam Targett, Satoko Yasuda, and Paul Wehman* 1131

## XV MEDICOLEGAL AND ETHICAL ISSUES

62. Medicolegal Aspects of TBI  
*Irvin V. Cantor* 1151
63. Ethical Issues in Clinicolegal Practice  
*Arthur Ameis, Nathan D. Zasler, Michael F. Martelli, and Shane S. Bush* 1163
64. Assessment of Response Bias in Clinical and  
Forensic Evaluations of Impairment Following TBI  
*Michael F. Martelli, Keith Nicholson, Nathan D. Zasler, and Mark C. Bender* 1183
65. Decision-Making Capacity After TBI: Clinical Assessment  
and Ethical Implications  
*Sunil Kothari and Kristi Kirschner* 1205
66. Life Care Planning After TBI: Clinical and Forensic Issues  
*Roger O. Weed and Debra E. Berens* 1223

*Index* 1241

# Preface

*Brain Injury Medicine: Principles and Practice* is designed as a comprehensive text for all clinicians dealing with the assessment, management, and rehabilitation of patients with traumatic brain injury (TBI) from “coma to community.” This book examines numerous aspects of brain injury with perspectives from an internationally respected group of authors, who include both “in the trenches” practitioners as well as researchers. We hope that this text will serve as a “go-to reference” for clinical practitioners to use in day-to-day practice, students and trainees learning about TBI, and other professionals who need to learn more about TBI and its management.

The text opens with a description of the clinical continuum of care and the natural history of TBI, followed by perspectives on rehabilitative care in the United States and other countries, with discussions on training and research. Public health issues are discussed with chapters on epidemiology and prevention. The effects of trauma and recovery on the brain are described in chapters on pathophysiology, brain plasticity, and treatments that may influence neural recovery. Readers will learn up-to-date information on technologies to assess TBI, including structural and functional neuroimaging

and electrophysiologic techniques. A series of chapters covers prognosis and outcome, including life-expectancy.

The bulk of the text deals with clinical care of patients with TBI—across the continuum of care, at different levels of severity, and among different age groups. There are discussions of the full gamut of medical assessment and management of neurologic, medical, physical, cognitive, and behavioral problems resulting from TBI. Given the biopsychosocial nature of TBI and its consequences, there are also chapters on the psychological, neuropsychological, psychosocial, ethical, and medicolegal aspects of this condition.

Ultimately, the 66 chapters in this comprehensive text will provide readers with a full complement of medical and interdisciplinary rehabilitation perspectives on the assessment and management of persons with mild to severe TBI. It is hoped that this text brings together knowledge, experience, and evidence-based medicine in a manner that will promote further cross-disciplinary practice and research in the field of TBI. Most of all, we hope that this book will result in individuals with TBI receiving timely and accurate assessments and appropriate management to optimize their outcomes as well as the quality of their lives and those who care for them.

*Nathan D. Zasler, MD  
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# Foreword

We are what our brains allow us to be. A traumatic brain injury (TBI) changes a person as an individual and has an impact on the ability to interact with his or her environment. The neurorehabilitation of persons who have had a traumatic brain injury requires an extraordinarily diverse knowledge base and expertise in order to optimize both neurological and functional outcome and minimize medical, as well as psychosocial, morbidity. In an ideal scenario, the neurorehabilitationist facilitates maximal community independence, patient self-reliance, and community re-integration relative to work, leisure, and social interactions while maintaining psychoemotional health.

TBI may cause changes that affect cognition, behavior, language, somatic function, and neuromedical status. Such an injury can have a negative impact on the complex biopsychosocial relationships that we all have in our environment. Brain injury, in and of itself, can create additional and unexpected problems depending upon the age of the individual at the time of injury. Sometimes, these problems may not be readily apparent early after an injury, but may instead develop later, as the child “grows into” brain injury problems. The neurorehabilitation process should ideally start in the intensive care unit and continue through optimal community reintegration and medical stabilization. For some patients, this stage never comes, and chronic care is therefore necessary.

The neuromedical and rehabilitative management of TBI demands a vast knowledge of a multiplicity of fields including neurophysiology, neuroanatomy, neuropathology, neurology, neuropharmacology, neuropsychiatry,

physiatry, psychology, neuropsychology, orthopedics, nursing, therapy specialties including occupational therapy, physical therapy, speech language pathology, and therapeutic recreation, among others. Based on extensive experience over the years, an interdisciplinary team approach clearly facilitates optimal neurorehabilitation. In order to optimize this process, all clinicians on the team must have a good understanding of how to optimize the efficacy of this treatment model and coordinate care in a manner that is most cost-efficient relative to achieving optimal functional outcomes.

Persons with TBI need to have a continuum of programs available in order to facilitate continuity of care and optimize their outcomes. The specific approaches may differ across the continuum of care, as might the medically indicated clinicians. Each of these stages potentially requires a different and evolving knowledge. Adequate appreciation of clinical nuances is paramount in being able to judge, document, and predict recovery and future neurorehabilitative needs. Functional gains can continue for years, even well after neurologic plateaus are reached. Even in scenarios where one finds that patients have functionally plateaued, there may still be opportunities to manipulate the environment and/or provide new treatment methodologies to further optimize quality-of-life and functional status.

Given the complexities in the medical management of this patient population and the need for a functional, holistic approach that utilizes a biopsychosocial model of care, clinicians need a source of information that brings together the myriad medical and allied health specialties

involved in understanding TBI care and rehabilitation. This is the importance of *Brain Injury Medicine: Principles and Practice*. This book will provide readers with the most recent information and methodologies to facilitate clinical practice and optimize patient functional outcomes. The text provides the knowledge necessary to understand what is happening at various stages of recovery following TBI and, more importantly, what needs to be done during each stage. It is an excellent resource for both clinicians and non-clinicians alike. Medical physicians involved in neurorehabilitation, such as physiatrists or neurologists, as well as other rehabilitation team members, will find this book an invaluable resource. Physicians who deal with TBI in a non-neurorehabilitation context

will certainly benefit from understanding brain injury from the perspective provided by this text, which will further facilitate use of rehabilitation resources in their own community. It is an outstanding and comprehensive book that can serve as the “bible” for each member of a team working with a TBI patient, allowing each of them to understand the reasons behind the decisions of their fellow team members.

We are what our brains allow us to be. The neurorehabilitation professional needs to have a standard by which to understand and advise patients, family members, fellow professionals, and payors regarding TBI-related issues. This book will significantly enable each professional to have access to this vast fund of knowledge.

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*Chapter 39: Psychological Approaches to  
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*Chapter 1: Clinical Continuum of Care and Natural  
History*

*Chapter 22: Mild TBI*

*Chapter 23: Post-Concussive Disorder*

*Chapter 38: Post-Traumatic Pain Disorders: Medical  
Assessment and Management*

*Chapter 39: Psychological Approaches to  
Comprehensive Pain Assessment and Management  
Following TBI*

*Chapter 63: Ethical Issues in Clinicolegal Practice*

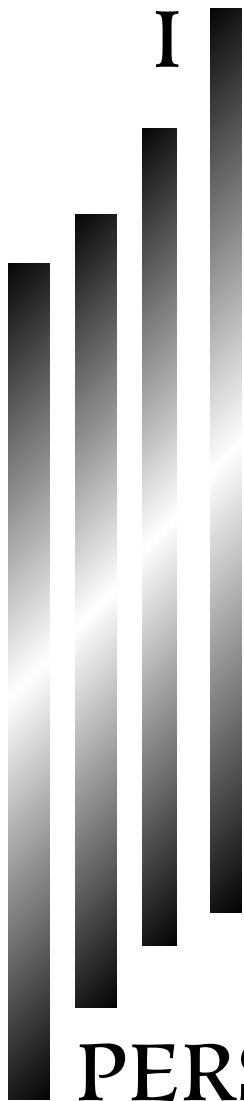
*Chapter 64: Assessment of Response Bias in Clinical  
and Forensic Evaluations of Impairment  
Following TBI*

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*Chapter 2: Brain Injury Rehabilitation: Past, Present,  
and Future?*



**PERSPECTIVES ON  
REHABILITATIVE CARE  
AND RESEARCH**

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# 1

## Clinical Continuum of Care and Natural History

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### **SCOPE OF THE PROBLEM AND THE CHARACTERISTICS OF TRAUMATIC BRAIN INJURY**

Systems of care for patients with traumatic brain injury (TBI) must account for the particular characteristics of this disorder. First, TBI is among the most common of serious, disabling neurological disorders. It is a significant problem in all societies. In the United States at least 1.4 million TBIs occur every year, and there are 5.3 million people living with disability from TBI (1–3). (See Thurman et al., Chapter 6, for a full discussion of the epidemiology of TBI). Systems of care must allocate resources for the large number of people who are affected by the disorder.

Second, TBI is largely a younger and older person's disorder (2). Individuals younger than 30, mostly males, make up the largest proportion of those affected. TBI usually impacts people who are in the later stages of adolescent development or in early adulthood. Therefore, TBI typically disrupts important periods of life involving educational and social development, emerging vocational productivity and adult independence, and beginning spousal relationships and family development. Older persons present particular problems related to aging including co-morbidities, slower and less complete recovery, and vulnerability to complications of injury and treatment (4) (see Englander et al., Chapter 21 on "The Older Adult").

Systems of care must address needs that include special educational requirements, independent living, vocational training and supports, and supports for family members.

Third, TBI commonly affects people with preexisting problems such as substance abuse, learning disabilities, behavioral disorders, psychiatric disorders and other risk factors that may make people more prone to injuries. In addition, persons with brain injury are more prone to psychiatric co-morbidities and psychosocial difficulties following injury. Systems of care must consider these pre-injury and post-injury issues with respect to injury prevention, their interactions with the clinical effects of injury and potential detrimental influence on recovery from TBI.

Fourth, the most important and consistent effects of TBI involve cognitive, emotional, and behavioral functioning. Motor and sensory perceptual problems also occur in varying amounts, more likely in those with more severe injuries. Cognitive and behavioral problems present more challenges to the health care system because they are often more difficult to recognize, characterize, and treat than traditional medical and physical problems. Persons with TBI, particularly less severe injuries, may not have any obvious physical markers of the injury, though there may be profound effects on the individual's ability to function, largely resulting from cognitive or behavioral dysfunction. Criteria for medical rehabilitation reimbursement, length of stay, and utilization decisions are

often more focused on motor issues affecting function and less focused on cognitive and behavioral treatment issues. Some insurance payers even exclude coverage for cognitive rehabilitation, although there is evidence to support its efficacy (5, 6) (see Cicerone, Chapter 41 on cognitive rehabilitation). Systems of care must focus on proper assessment and treatment of cognitive and behavioral problems, even though they may not fit the characteristics of medical rehabilitative systems that were originally developed for medical and physical disabilities (see Chapters 41–45).

Fifth, TBI, especially more severe injuries, can have a relatively extended natural history and lifelong effects. Recovery from TBI may be more protracted, over a relative longer portion of the lifespan, than most other acquired injuries or neurological disorders that evolve more quickly or typically affect persons at later stages of life. Thus, systems of care for TBI need to recognize the potentially prolonged recovery timetable. Further, recovery after TBI has a somewhat predictable and characteristic course, with a variety of recognizable cognitive, behavioral, and sensorimotor syndromes at different stages. An appreciation of the natural history of TBI is essential to assessing the individual and to effectively applying treatment and services at different stages of recovery, as well to avoiding treatment that may be unnecessary or ineffective (see discussion on natural history below).

Finally, TBI is a disorder with a wide variety of pathophysiological effects, a range of severities, and a multitude of problems that may occur as the result of injury. Persons with apparently similar injuries may have significant variation in their presentation, course of recovery, response to interventions and ability to return to functioning. Systems of care should have a breadth of treatments and services to address the variety of problems that can occur after TBI, and the flexibility to move persons through the system in different ways depending on their individual needs at different times post-injury.

## THE DEVELOPMENT OF SYSTEMS OF CARE

The provision of a comprehensive continuum of care for persons with TBI is an enormous challenge given the characteristics of TBI outlined above and the wide range of services that should be provided to large numbers of people, over relatively longer periods than most other disorders. The challenge confronts many groups: persons with TBI and their families; clinicians managing the care of the patient with TBI; service providers attempting to provide efficient and effective care; health insurance providers; public and other payers balancing coverage needs with financial pressures; and society at large, making choices about resource allocation and costs. Resources for patients with TBI include: acute and post-acute medical

care; rehabilitative services in the hospital, at home, in the community, and in residential settings; psychosocial services; educational and vocational services; and a variety of other support services.

The development of systems of care for persons with TBI evolved in the 1970s and 1980s. In part, the systems that developed for care of patients with TBI were influenced by systems of care that were developed for those with spinal cord injury (SCI). Prior to development of specific programs for persons with TBI, patients were frequently treated in psychiatric facilities, nursing homes, or more general rehabilitation facilities. The Rehabilitation Services Administration and NIDHR (which was to become NIDRR), which had funded SCI model systems in the early 1970s, also funded two model system projects for TBI in 1978 at Stanford University and New York University (7). The recommendations from these projects helped to promote the development of interdisciplinary, dedicated TBI programs with services across the continuum of recovery. As programs began to develop, the lack of organized planning led to an initiative by the NIDRR under the Department of Education in 1987 to fund five TBI model systems demonstration projects (8). This has expanded to sixteen TBI Model Systems Projects throughout the country in part aimed at gathering information to improve comprehensive systems of care for patients with TBI. The components of these model systems of care includes emergency medical services, acute neurosurgical care, comprehensive rehabilitation services, long-term interdisciplinary follow-up and rehabilitation services, as well as what were termed optional services, including behavior modification programs, home rehabilitation services, case management and community living options (8). A key portion of this program has been longitudinal and project specific based research.

Beginning in the mid-1980s, the Commission on Accreditation of Rehabilitation Facilities (CARF) developed standards for TBI rehabilitative care by establishing specialized accreditation for TBI programs. It now accredits TBI programs in six categories: inpatient, outpatient, home- and community-based, residential, long-term residential, and vocational.

An important development in TBI care was the TBI Act of 1996 passed by Congress to “provide for the conduct of expanded studies and the establishment of innovative programs with respect to traumatic brain injury.” Four provisions of the Act included surveillance and prevention under the CDC; basic and applied research to improve diagnosis, therapeutics and the continuum of clinical care conducted by the NIH; a planning and implementation grant program to the states under the Health Resources and Services Administration (HRSA); and a Consensus Conference conducted by the Center for Medical Rehabilitation and Research at NIH (9). The NIH consensus conference panel addressed the continuum of

care for TBI in their conclusions. The recommendations included that “persons with TBI should have access to rehabilitation services through the entire course of recovery, which may last for many years after the injury” and that “community-based, non-medical services should be components of the extended care and rehabilitation available to persons with TBI” (10).

## REALITIES OF THE MARKETPLACE

Although demonstration projects such as the TBI Model Systems have presented apparently effective systems of care for persons with TBI, the realities of the marketplace in the United States have presented challenges to providing such care and services to all those in need. Corrigan outlined 20 important challenges to meeting the needs of persons with TBI, within the categories of access, availability, appropriateness, and acceptability (9). With regard to access, the problems involve identifying and utilizing services, even if they are available. There may be difficulties accessing information about available resources. Sometimes it is difficult to determine what resources are covered by health insurance, and sometimes coverage is denied even after services are delivered. Families and care providers usually lack roadmaps to guide access to appropriate resources, and points of entry into publicly funded systems may be unclear. Service systems may have artificial barriers created by narrow eligibility criteria. Services are often fragmented and not well coordinated.

Corrigan pointed out a number of availability issues for which the main limiting factor is funding. Health insurance may not cover needed services that are available, or may direct individuals to centers that are less familiar with the care of persons with TBI. Further, lack of payer support may preclude the availability of some services to begin with. Many persons with TBI have no health care funding at all at the time of injury, and present state budget constraints are further threatening the Medicaid program. When available, health insurance typically fully covers acute care, but coverage for rehabilitative care becomes incrementally more difficult across the continuum of care, from inpatient to outpatient to residential and community services. Health insurance coverage also tends to be more restrictive for cognitive and behavioral services as opposed to more traditional physical rehabilitative and medical treatment. In many cases, coverage for services has to shift from private to public sources such as Medicaid and Medicare over the course of recovery because of limits in coverage for longer term care in many policies. Public funding has further restraints on long-term coverage. Several states have developed a system of Medicaid waivers to provide long-term home and community-based services that would otherwise be covered only for institutional settings, such as nursing

homes. The fragmentation and limitations in financing of care and services can create a nightmare of coordination for persons with brain injury, their families, and service providers. Clinicians who coordinate care for persons with brain injury must become aware of the complexities of reimbursement and the array of alternative sources of funding for TBI care and support in their community.

Other issues affecting the availability of services include geographic limitations; lack of transportation; a paucity of appropriate, affordable housing; limitations in resources for behavioral problems in children with special needs; and the long-term needs of persons with TBI (9). Patients with TBI in rural communities have special challenges in finding services within a reasonable distance. Even when available in a nearby area, transport to and from these services can be a major problem, and home services may not be available or sufficiently expert for this population. The ability to provide a full array of services to all age groups within a reasonable proximity, with full funding support, is an enormous challenge that may never be fully satisfied.

The appropriateness of available resources is also a common problem. Sometimes the reason for inappropriate services is dictated by payer constraints. For instance, because the main payer for long-term care services is Medicaid, if waivers to support home and community services are not available, patients with TBI who cannot return home may be placed in nursing homes, even though community-based services may be more appropriate. Even if services are available, programs and professional providers may lack the knowledge and expertise to serve this population. Generalists in a particular discipline or specialty may not have the skills for proper assessment or treatment of the patient with TBI. Accreditation programs such as CARF and the American Academy of Certified Brain Injury Specialists (AACBIS) have attempted to set standards and credentialing to assure appropriateness of programming and expertise. (See also Chapter 4 on training and certification.) Nevertheless, such expertise may simply not be available in some geographic areas or at certain levels of care. Sometimes erroneous services are applied because of this lack of expertise, but at times services may be improperly or needlessly applied even by those with expertise. Inaccurate diagnosis, inappropriate application of treatment at a particular stage of recovery, use of unproven or ineffective treatments, or application of effective treatment to those for whom it would not be of benefit are examples. Use of accurate diagnosis and prognosis is necessary to avoid some of these problems of inappropriate treatment (see below on natural history). Sometimes services are not fully relevant to a person's and family's needs at a particular time or in a particular environment. The acceptability of these services to the goals of the person with TBI and how services promote the persons self-actualization is another challenge to the TBI service marketplace (9).

### ESSENTIAL COMPONENTS OF THE CLINICAL CONTINUUM

The continuum of care for patients with TBI occurs in a variety of settings. Figure 1-1 illustrates the different types of care and how patients may move through these components. The flow through these services may not be linear. Patients may enter or leave the system of care at different points, or reverse directions, based on individual needs or the dictates of the marketplace.

#### Prevention

The earliest aspect of the care continuum involves public health issues prior to injury occurrence. Injury prevention is an essential part of trauma care systems. The TBI Act of 1996 charged the CDC with the responsibility for prevention, in addition to surveillance, to assess factors that increase the risk of TBI and those that are protective. Injury prevention programs generally include three components: programs designed to alter behavior and improve decision-making to increase self-protection; product improvement to minimize the chance of injury or protect the individual

in an accident; and legislation and public policies that require individuals to follow safety guidelines. Prevention of TBI includes a number of efforts such as reducing alcohol-related injuries, preventing falls, preventing violence, promoting safe practices in sports, promoting helmet and seatbelt use, enhancing safe driving practices, and improving vehicle safety. (See Napolitano et al., Chapter 7, for a discussion of primary prevention.)

#### Emergency Medical Services

Since the 1980s, emergency trauma systems have developed throughout the United States and have led to improved survival and recovery (11–13). Mortality for those that reach the hospital has been reduced from nearly 50% to about 25% (13). Regional trauma systems have developed to promote quick evacuation using ground or air transport to level I and level II trauma centers from the field, or from level III and IV trauma centers when necessary for more serious injuries. The level I and II trauma centers have full-time intensive care, imaging, neurosurgical, and other trauma subspecialists. The Brain Trauma Foundation’s (BTF) Guidelines for Prehospital

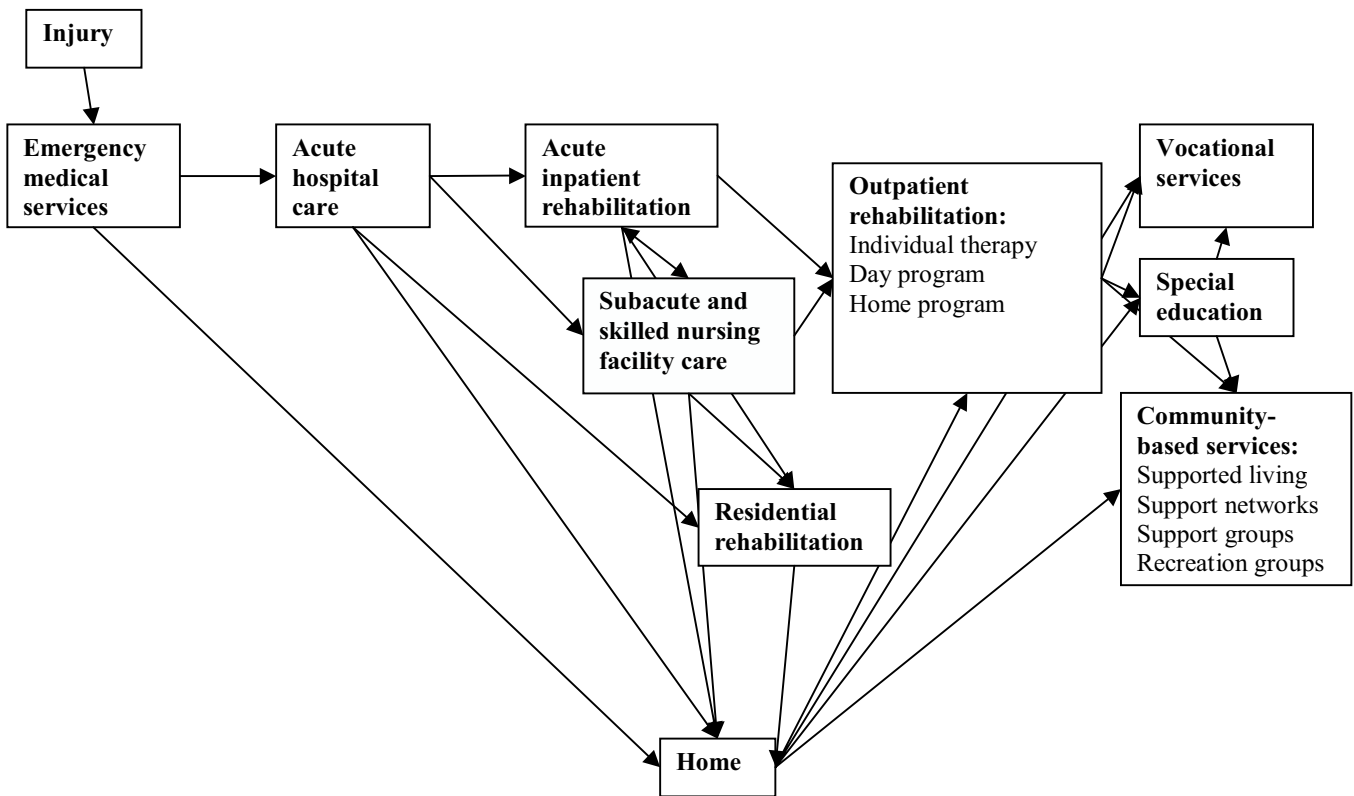


FIGURE 1-1

Usual flow of patients through the clinical continuum of care. Choices of services and direction of flow will be based on severity, stage of recovery, patient’s needs, availability of resources, availability of home and community supports, and constraints of the marketplace

Management of Traumatic Brain Injury have played a role in improving emergency prehospital care (12). Although improved, proper diagnosis, patient education, and referral for appropriate follow-up is still lacking for many patients (14).

### **Acute Hospital Care**

Patients with TBI who are admitted for acute hospital care range from those who need a period of observation to recognize secondary neurological deterioration and neurosurgical complications that may ensue after a delay, to those with co-morbidities that require hospital care, to those with more severe brain injury that requires intensive care management. Acute neurosurgical and intensive care for patients with TBI have improved over the last two decades with better survival and outcomes (15). Evidence-based guidelines for acute TBI care, including the use of intracranial pressure monitoring, have contributed to better outcomes (16–18). (See also Chapters 18 and 19 on acute care.)

Rehabilitation assessment and early rehabilitative interventions should take place a short time after admission, in the acute hospital setting. Subsequent decisions for rehabilitative care are made as the patient progresses toward medical and surgical stability, when the severity of the injury and the clinical rehabilitation needs become more apparent. The pathway toward acute inpatient rehabilitation versus outpatient or subacute care is largely based on injury severity and pace of recovery. Generally, patients with severe injuries (e.g., unconsciousness for a day or more, or post-traumatic amnesia and confusional states of at least days to weeks, or patients with large focal lesions) move to acute inpatient rehabilitation facilities. Constraints related to marketplace issues may affect this decision. For instance, some health care plans will not support admission to inpatient rehabilitation facilities if a patient has few traditional physical rehabilitation needs (e.g., needs little or no help ambulating) even if the patient has profound cognitive and behavioral disturbances related to the injury. Patients with mild injuries generally return home and may need outpatient rehabilitation services. A proportion of patients with moderate injury may benefit from at least a brief inpatient rehabilitation stay, depending on their circumstances. Patients who are slower to recover may require extended care in the acute hospital, or be transferred to subacute or skilled nursing facility (SNF) care instead of inpatient rehabilitation. In many systems such persons may be lost to the follow-up of those with a primary interest in caring for patients with TBI. Strong consideration should be given to transferring such patients to facilities with special expertise in the assessment and care of patients who are unconscious or minimally conscious (usually in acute inpatient rehabilitation or specialized subacute facilities), because these

patients are vulnerable to secondary complications and may have significant potential for further recovery, albeit at a slower pace.

### **Acute Inpatient Rehabilitation**

Acute inpatient rehabilitation may occur on general rehabilitation units or in dedicated brain injury units that are within acute care facilities or part of freestanding rehabilitation hospitals (inpatient rehabilitation facilities or long-term care hospitals). Admission criteria to hospital-based acute inpatient rehabilitation involve the following:

1. an intensity of medical and nursing care needs that requires full-time physician monitoring and specialized rehabilitative nursing expertise;
2. functional deficits that would benefit from a higher level of rehabilitation treatment intensity (usually designated at a minimum duration of 3 hours a day).

Patients are best served in programs dedicated to brain injury care or those with a significant proportion of staff with expertise in managing brain injury. Rehabilitation teams usually include: case managers; physical, occupational, and speech therapy staff; rehabilitation nurses; nursing assistants; psychologists; neuropsychologists; rehabilitation physicians (usually a physiatrist, rehabilitation neurologist, or neuropsychiatrist); primary care physicians; and a variety of other consultant medical specialists. Other disciplines such as social workers, rehabilitation technicians, therapy assistants, behavior specialists, recreation therapists, other subspecialty therapists, chaplains, and attorneys may also contribute to care.

Expertise in managing behavioral problems and assuring patient, family and staff safety is important because patients in agitated confusional states are usually managed at this level of care (see below). Family education to familiarize them with the problems and needs of persons with brain injury is essential at this level of care, especially for those that will transition home from acute inpatient rehabilitation. The decision regarding the next level of care depends on the patient's medical stability, level of dependency, safety, and whether the person's needs can be adequately met at home or requires further institutional care. Patients with severe TBI typically still require some supervision and, perhaps, physical assistance for self-care and mobility when they are ready to be discharged from acute inpatient rehabilitation.

### **Subacute and Skilled Nursing Facility Rehabilitation**

Patients with TBI are usually admitted to this level of care from acute hospital care or acute inpatient rehabilitation. Therapies are provided at a lower level of intensity than in



acute inpatient rehabilitation and the level of medical monitoring is less frequent than acute inpatient rehabilitation. There are many programs at this level that specialize in neurorehabilitation and it is certainly preferable if this level of care occurs in programs with special expertise in brain injury management. Specialized neurobehavioral treatment units in SNFs are available in some areas for patients with more persistent behavioral regulation problems.

As noted above, some SNFs may offer specialized care for patients with TBI with prolonged impairments of consciousness. The availability of specialized subacute and SNF facilities may be limited in some areas because of market constraints. Care for the needs of TBI patients in these settings may be costly, exceeding the usual reimbursement standards for this level of care. Alternative funding sources or variance in reimbursement standards may be necessary to maintain more specialized subacute or SNF care.

Often, SNF level rehabilitation care takes place in more general facilities, and frequently younger patients with TBI are in the minority among an older group of patients with other disorders, such as dementia. Lengths of stay at this level of care varies but usually lasts one or more months; a minority of patients transition to unskilled residential levels of care at the same facilities. A large proportion of patients transition home and may go on to outpatient rehabilitation or other outpatient services.

### **Outpatient Rehabilitation**

Outpatient rehabilitation can take on a number of different forms. Sometimes it consists of individual therapies involving physical, occupational and speech therapists. There may be other available services including psychology, neuropsychology and therapeutic recreation. The team may be led by a case manager, and they may provide other coordinated activities such as group treatments. Usually rehabilitation at this level is less coordinated than inpatient treatment and therapists provide care more autonomously. This type of care may occur in the setting of the home through visiting nurse or other agencies, or on the premises of an acute hospital, a rehabilitation hospital, or an outpatient rehabilitation facility.

A more coordinated form of outpatient rehabilitation may take place in a day program, with a full array of therapies, group treatments and group activities, case management, and regular team meetings to set goals and review progress. More holistic programs may include a psychotherapeutic milieu associated with the therapy programming. These programs are often in naturalistic, community settings and take advantage of this location to set up activities to foster community reentry treatment goals.

The length and intensity of treatment is determined by the patient's needs but is largely constrained by health insurance payer contracts and public funding policies limiting duration of care and range of covered services.

Following outpatient rehabilitation, additional community-based services may be provided.

### **Residential Rehabilitation**

Group residence programs may provide services at various stages after injury. These programs may offer individual therapies and group therapies, as well as resources to foster independent living skills. Residential programs may be aimed at patients recently discharged from acute hospital settings or acute inpatient rehabilitation, or those later in the process of recovery who cannot be in their own home setting, and who require a structured, supervised setting and specialized programming cannot be in their own home setting. There are usually only part-time nursing services and programs may or may not provide physician services. Those states with more generous auto insurance benefits tend to have more extensive residential programs. Staffing includes a mix of professional therapists, other professional disciplines, and lay staff. Patients may progress in levels of independence in these setting and go back home or to other long-term living arrangements, such as supported living (see "Other Community-Based Services" below), after this level of care.

### **Vocational Services**

For most persons with TBI, the return to work is the most important long-term rehabilitation goal and measure of treatment success. Returning to some sort of productive activity is an essential part of societal reintegration and life satisfaction after brain injury and an important part of the continuum of care. In the United States, the states receive federal money to operate vocational rehabilitation programs to provide vocational rehabilitation services to individuals with disabilities. Services support reeducation, training and worksite support services. Even those with severe injuries, who may not qualify for regular marketplace jobs, are eligible for services under this mandate. Supported employment has become one of the important vocational rehabilitation strategies for getting persons with disabilities back to employment in regular work sites. These services are most successful when coordinated with outpatient rehabilitative care and assessments. Many of these programs have been underfunded and it has been a problem to provide the intensive ongoing supports that are necessary to keep some persons with TBI employed. Many states have adopted innovative programs to extend funding using resources such as Medicaid waivers to improve services and employment retention (19).

### **Special Education**

Education services are a necessary component of the continuum of care for children and adolescents with TBI.

TBI became a part of the federal Individuals with Disability Education Act in 1990. This federal law mandates that the education needs of school age children with TBI, among other disabilities, will be provided in the public schools and must include any necessary rehabilitation services. Services should be planned and monitored using an individualized educational program (IEP). Students often transition from inpatient or outpatient rehabilitation to school-based services, sometimes beginning with home tutoring. Ylvisaker and colleagues have made a number of recommendations for assessment, intervention, student support, educator training, family support and system flexibility to better serve the particular educational and rehabilitative needs of students after TBI (20).

### **Other Community-Based Services**

Persons with TBI may require other ongoing care and support after formal rehabilitative care has ended. These home and community-based services are more fragmented and less readily available. Patients who are unable to live independently, and who are not relying on home supervision by family or friends, require supported living environments. Previously, because Medicaid has been the primary funder of long-term care, this meant placement in nursing homes, usually a poor alternative for younger persons with TBI. A growing number of states with Medicaid waiver programs have been able to provide supported living services in the community using such models as supervised group homes, foster homes, and personal care attendants. A number of other models have been developed.

Community support networks and support groups for persons with TBI and their families are important resources. One such support network, the Clubhouse Model, adapted for persons with TBI in the 1980s from the psychiatric community, provides a setting for members and volunteers to participate in social, recreational, and work-related activities. It has been a cost-effective method to promote practical, functional living skills. Support groups for persons with TBI and their families are often sponsored by state chapters of the Brain Injury Association of America (BIAA).

Other necessary community services include provisions for transportation for those who are unable to drive or ride public transportation. Respite care to provide time-off for full-time caretakers of persons with severe disability after TBI is another important need. Legal services, financial and estate planning, mental health services, and treatment of substance abuse must also be considered part of community-based system of care for people with TBI.

### **Case Management**

Fragmentation and lack of coordination of care is one of the major problems in finding and applying proper

services for the individual with TBI. Case managers within institutions and in the community play an essential role in coordinating services. Case managers collaborate with others, including patients, families, providers, and payers to assess, plan, implement, coordinate and monitor services to meet an individual's needs and promote favorable outcomes in a cost-effective manner. In addition to coordinating care within the TBI system, case managers must coordinate treatment in other areas such as chronic pain, mental health and other medical specialty areas. Case managers and life care planners may develop proposals outlining the anticipated lifelong care needs of persons with TBI (see Weed and Berens, Chapter 66, on life care planning).

### **SERVICE DELIVERY IN RELATION TO NATURAL HISTORY OF TBI**

Accurate diagnosis and an appreciation of the natural history of TBI are useful in formulating treatment plans and assuring appropriateness of services along the continuum of care. This effort involves assessing a person's brain injury in the context of pathophysiologic damage, associated clinical neurobehavioral syndromes, stage of recovery and anticipated course of recovery, based on knowledge of brain-behavior relationships and natural history (21). The formulation must also consider interaction with non-injury factors such as age and psychosocial issues, associated injuries, premorbid problems, co-morbidities, and later complications.

This understanding helps in determining where the patient is along the path of recovery and in projecting expectations for subsequent recovery to inform treatment planning with respect to treatment setting, treatment strategies, treatment goals, and length of stay. It may also help avoid unnecessary treatment of problems that may be expected to resolve as part of the natural course of recovery (e.g., post-traumatic amnesia or confusional agitation) or impairments with a poor prognosis that may not recover with direct treatment (e.g., amnesia after extensive, bilateral hippocampal injury or behavior dysregulation after massive bilateral orbital prefrontal and temporal polar damage).

Such an understanding of natural history also helps determine when clinical syndromes do not fit the expected path of recovery, suggesting possible secondary neurological complications (e.g. hydrocephalus, chronic subdural hematomas), the influence of noninjury factors (medical, iatrogenic or psychogenic), or misdiagnosis of injury type and severity. The clinical natural history of TBI can be defined in the context of focal or diffuse neuropathologic events. (See Kochenak et al., Chapter 8, for an extended discussion of TBI neuropathology.) The critical pathophysiologic factors are the type, distribution,

severity, and location of these combined neuropathological events after brain injury.

Although focal and diffuse pathological processes are often intermingled and have common secondary and metabolic consequences, it is useful to consider them separately for the purposes of clinical diagnosis. The precision of diagnosis varies and may be challenging, especially with respect to diffuse and secondary injuries, for which there are as yet no readily available, direct clinical, diagnostic probes.

### Diffuse Injury

Diffuse axonal injury represents the main diffuse pathological process, but it is associated with a host of associated pathophysiological phenomena (see Chapter 8). The natural history of diffuse injury is characterized by a recognizable pattern of stages that occur across the wide spectrum of severity. Injury severity determines the duration of recovery stages and levels of impairment at each stage of recovery. These stages can be combined into three principal phases of recovery from the acute to chronic stages:

1. loss of consciousness (LOC);
2. post-traumatic confusion and amnesia (PTA);
3. post-confusional restoration of cognitive function.

These form the basis for the main indices of clinical severity for TBI. These indices can help project a rough approximations for the time course of recovery and the probabilities for a particular outcome (22–26). The three phases of recovery appear to be proportionally related in patients with diffuse injury; each subsequent phase is typically several-fold longer than the previous one (22). Their proportionality in patients with diffuse injury, although variable, can contribute to predicting the time course of recovery. For instance, there was a predictable relationship between the duration of unconsciousness (LOC) and duration of confusion/PTA in a series of patients with diffuse injury defined by a linear regression model that predicted nearly 60% of the variance —  $PTA (wks) = 0.4 \times LOC (days) + 3.6$  (22). This model was confirmed in a separate cohort of 228 patients (27). Longer PTA was observed in older patients, especially over age 40, or if a focal frontal lesion was present. Predicting PTA may aid rehabilitative treatment planning with respect to length of stay decisions, treatment choices for confusional agitation, and other treatment issues at this stage of recovery.

Patients with the least severe diffuse injuries (mild concussion) evolve through LOC (if complete loss of consciousness occurs at all) in seconds to minutes and through PTA usually in minutes to hours, followed by a post-confusional phase typically lasting days to weeks. In

mild TBI the transition through the earliest stages may be brief, unwitnessed, and difficult to document. Patients with severe TBI may require days to weeks to evolve through LOC, weeks to months to resolve confusion and PTA, and months to years to evolve through the post-confusional residual recovery phase. The course of recovery after severe TBI is among the longest observed after neurological damage. Dynamic changes in neuropsychological functioning have been observed as long as 5 years post-injury (28–31). Some patients with very severe injuries may stall in recovery at some stage in this process (e.g., permanent vegetative state (32) or minimally conscious state (33).

This pattern of recovery has been delineated in stages according to various schemas. The most widely used is the Rancho Los Amigos levels of cognitive functioning (34). (See Table 1-1.) Another schema, first proposed by Alexander (35) and further modified (referred to as the Braintree scale) (21, 36), follows more traditional neurological nomenclature. (See Table 1-2.) As patients progress through these stages the principal defining cognitive limitations evolve from deficits in arousal and consciousness, to basic attention and anterograde amnesia, to higher-level attention, memory, executive functioning, processing speed, insight, and social awareness (37).

The first stage of recovery is *coma*, a state of unconsciousness without spontaneous eye opening. This corresponds to Rancho level I. Patients with diffuse axonal injury are unconscious at the outset, without lucid interval. The depth of coma in the time period shortly after injury, as measured by the Glasgow Coma Scale (GCS), is one of the common markers of injury severity and prognosis.

Almost all persons with severe TBI who survive resume spontaneous eye opening and sleep/wake cycles while still unconscious, a condition termed a *vegetative state* or Rancho level II. Except for the small percentage of very severely injured patients who remain permanently vegetative, evidence of awareness and purposeful behavior resume, often heralded by visual fixation and tracking. The ability to follow commands is the usual convincing

**TABLE 1-1**  
*Rancho Los Amigo Levels of Cognitive Functioning After TBI (34)*

I.	No response
II.	Generalized responses
III.	Localized responses
IV.	Confused – agitated
V.	Confused – inappropriate
VI.	Confused – appropriate
VII.	Automatic – appropriate
VIII.	Purposeful and appropriate

**TABLE 1-2**  
***Braintree Neurologic Stages of Recovery from Diffuse TBI (and corresponding Rancho Los Amigos Scale Levels) [settings of care]***

1. *Coma*: unresponsive, eyes closed, no sign of wakefulness (Rancho 1) [emergency medical services; acute inpatient hospital]
2. *Vegetative state/wakeful unconsciousness*: no cognitive awareness; gross wakefulness, sleep-wake cycles begin (Rancho 2) [acute hospital; acute inpatient rehabilitation; subacute rehabilitation]
3. *Minimally conscious state*: inconsistent, simple purposeful behavior, inconsistent response to commands begin; often mute (Rancho 3) [acute hospital; acute inpatient rehabilitation; subacute rehabilitation]
4. *Confusional state*: interactive communication and appropriate object use begin; amnesic (PTA), severe basic attentional deficits, hypokinetic or agitated, labile behavior; later, more appropriate goal-directed behavior with continuing anterograde amnesia (Rancho 4, 5, partly 6) [acute hospital; acute inpatient rehabilitation]
5. *Post-confusional/emerging independence*: marked by resolution of PTA; cognitive impairments in higher-level attention, memory retrieval and executive functioning; deficits in self-awareness, social awareness, behavioral and emotional regulation; achieving functional independence in daily self care, improving social interaction; developing independence at home (Rancho 6 & partly 7) [acute inpatient rehabilitation; subacute inpatient rehabilitation; outpatient rehabilitation; residential treatment; outpatient day hospital and community reentry]
6. *Social competence/community reentry*: marked by resumption of basic household independence; developing independence in community, household management skills and later returning to academic or vocational pursuits; recovering higher level cognitive abilities (divided attention, cognitive speed, executive functioning), self-awareness, social skills; developing effective adaptation and compensation for residual problems (Rancho 7& 8) [outpatient community reentry programs; community-based services – vocational; special education; supported living services; mental health services]

marker of restored consciousness. Almost all patients with some loss of consciousness will be evaluated and treated by emergency medical services. Those with brief alterations of consciousness (e.g., seconds or minutes) may be discharged home. Patients with more prolonged LOC or more complicated injuries (e.g., focal lesions, other injuries) will likely be admitted for acute inpatient care, often beginning in surgical intensive care units, usually supervised by neurosurgical or surgical trauma specialists.

For patients recovering slowly, cognitive responsiveness may begin erratically and inconsistently, without any reliable interactive communication. This stage may be called a *minimally conscious state* and corresponds to Rancho level III (33). Many patients at this stage will continue in acute medical care settings and some who are slower to recover will transition to rehabilitation facilities, including acute inpatient rehabilitation, subacute rehabilitation, long-term care hospitals or skilled nursing facilities. (See also Chapter 25 on disorders of consciousness.)

When purposeful cognition is unequivocally established, basic attention and new learning remain severely impaired. This clinical condition may be labeled a *confusional state* and corresponds to Rancho levels IV, V, and part of VI. At this stage, patients are often highly distractible, with poorly regulated behavior. They may rapidly escalate to agitated behavior (Rancho IV). Less often, patients may remain in a state of underactivated, hypokinetic, withdrawn behavior. Dense anterograde

amnesia also defines this stage; patients are disoriented, have little or no moment-to-moment episodic recall and display little or no ability to learn new information after even a brief delay (posttraumatic amnesia). As this stage evolves, patients are better able to focus attention and regulate behavior (Rancho V). The end of this stage is characterized by a significant improvement in focused and sustained attention, reliable orientation, and resumption of continuous, day-to-day memory, albeit still somewhat defective (Rancho VI). Patients at this period of recovery are appropriate for care in dedicated TBI units in acute inpatient rehabilitation. Towards the end of this period of recovery, transition to home and outpatient rehabilitation programs should be contemplated. Patients who are transitioning slowly, or who still require significant amounts of supervision and assistance that may not be feasible at home, may require continued institutional treatment, perhaps at a skilled nursing facility or a residential treatment facility. Some may transition to an outpatient day program.

The *post-confusional* stages of recovery are characterized by a gradual improvement in cognitive and behavioral functioning in those with more severe injuries. This phase of recovery may be further broken into stages of *emerging independence*, as patients' cognitive abilities, self-awareness, and insight allow independence in self-care and safe unsupervised activity at home (Rancho level VII), and a stage of *social competence and community reentry*, with restoration of the capacity for independent function in the community or at the higher-level demands

of school or the workplace (Rancho level VIII). Services at these stages of care include outpatient therapies, day programs, community-reentry programs, residential treatment, and a variety of community-based services.

### Focal Injury

Focal cortical contusions, deep cerebral hemorrhages, and extraaxial (subdural and epidural) hemorrhages make up the majority of focal lesions after TBI. The time course of natural history of focal injury resembles that of vascular lesions of other causes, particularly hemorrhagic stroke, but the clinical consequences of focal injury after TBI are characteristic, owing to the predilection of lesions in the anterior and inferior portions of the frontal and temporal lobes. The acute phase involves edema and other early secondary pathophysiological phenomena which are maximal over the first few days post-injury. The resulting effects may include confusion and, perhaps, decreased arousal, especially if a mass effect compromises diencephalic and mesencephalic structures. Otherwise primary focal pathology is not directly associated with loss of consciousness.

As edema and other secondary effects wane over the first three weeks, more specific localizing effects of focal damage become more apparent. Recovery during this subacute phase is maximal over the first 3 months, but improvement may continue at a slower rate over many months. The size and depth of focal lesions, their laterality and the potential for reorganization within the neural networks affected by the damage, all in large part determine the time course and outcome.

Damage to limbic neocortical and heteromodal areas of the frontal and temporal lobes determines the usual effects of focal TBI on cognitive and behavioral functioning. The residual syndromes of prefrontal lesions include alterations in affect and behavior (e.g., disinhibition or apathy) impairment in attention, working memory and memory retrieval, and dysfunctional higher-level cognition (e.g., executive functions, insight, social awareness). Lesions in anterior and inferior temporal areas may also contribute to affective and behavioral disturbances. Larger lesions extending to medial temporal areas may produce specific impairments in memory encoding and retrieval (amnesia). Other localizing temporal syndromes involve extension of lesions into auditory association areas (e.g., aphasia, with left hemisphere lesions) and visual association areas (e.g., visual agnosias, especially with bilateral lesions).

The clinical syndromes associated with focal lesions are often embedded in the evolving effects of diffuse injury, if both types of injury are combined. Particularly with more severe and diffuse injuries, the overall outcome is driven largely by the effects of diffuse rather than focal injury (38). In patients with mild to moderate diffuse injury, large focal lesions may have more influence on recovery (39–41). Characterization of the localizing

syndromes associated with focal lesions may be difficult until unmasked after resolution of post-traumatic confusion. Another difficulty in isolating the effects of focal lesions is that neurobehavioral syndromes may be identical to those related to diffuse injury (e.g., dysexecutive syndrome, behavioral dysregulation) because these same areas, especially their axonal projections, are affected by diffuse pathology (42).

Although the problems may be similar, recovery and prognosis may be different. For instance, features of the frontal lobe syndrome, may be more persistent in patients with frontal contusion (43, 44). Levin et al. (45) observed that although other aspects of recovery were similar, unilateral frontal lesions adversely affect psychosocial outcome in children with TBI compared to those without focal frontal lesions. These aspects of diagnosis and prognosis related to focal lesions should also help inform rehabilitation planning. For example, behavioral regulation problems related to bilateral frontal and temporal focal lesions may be more persistent and thus demand more active early intervention and treatment planning over a longer horizon than similar problems that might occur after diffuse injury, which may be expected to resolve more successfully as the stages of recovery evolve.

### SUMMARY AND CONCLUSIONS

The provision of a continuum of care for persons with TBI is an enormous challenge given the numbers of people affected by the disorder (patients, family members, and others), the potential long-term course of recovery, the possible life-long effects (often beginning at an earlier stage of life), and the wide variety of types of brain damage, clinical effects, and associated problems. Systems of care for TBI involve coordination of numerous services utilizing many disciplines across the range of severities and course of recovery. These services include prevention; emergency, acute, early, and later rehabilitation; vocational, educational, and community support; and long-term care. A number of marketplace factors constrain the full development and availability of components of these systems for persons in need, most notably cost, payer support, and availability of resources. These constraints become progressively restrictive for services and supports beyond the acute treatment period.

An understanding of brain injury, its clinical consequences, associated problems and complications, and natural history of recovery helps in applying proper services for patients along the continuum of care, and helps assure more effective use of resources. Ongoing efforts at fruitful research to determine which interventions are most effective, for whom, and at what periods of time, will be essential to refine the best clinical practices possible along the continuum of care.

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# 2

## Brain Injury Rehabilitation: Past, Present, and Future?

*George A. Zitnay*

The ways that persons with disabilities have been viewed by society have changed significantly over the years, due mainly to economic, cultural, religious, and scientific influences. In most cultures, both in ancient and in earlier modern times, persons with a disability were negatively valued. Wolf Wolfensburger (1972) noted that historically persons with disability have been viewed as deviant. In ancient Greece and Rome, among Eskimos, and in Nazi Germany infanticide, abandonment, and extermination have been practiced on those perceived as deviant. Even in the United States, the U.S. Supreme Court upheld the states' right to sterilize persons with mental disability. Chief Justice Holmes declared "It is better for all the world, if instead of waiting to execute degenerate offspring for crime, or to let them starve for their imbecility, society can prevent those who are manifestly unfit from continuing their kind. [Three] generations of imbeciles are enough." *Buck v. Bell*, 274 U.S. 200 (1927).

Since earliest colonial times in America, persons with disabilities have been treated as offensive and frightening. Removal from society has been the way these individuals have been dealt with. During the Industrial Revolution, however, a degree of humanitarianism began to creep into the mainstream views of society as the incidence of occupational injuries increased. This was fueled by increasing public awareness about the issues of child labor, poor working conditions, and the large and growing number

of persons sustaining occupational injuries that left them with permanent disability. During World War I, the public concern over the large number of injured soldiers without means of support spurred on the creation of federal rehabilitation policies for military personnel.

Early pioneers in the emerging field of rehabilitation included Thomas Hopkins Galludet, who brought manual communication to Americans with speech and hearing impairments; Louis Braille, who developed a touch system for reading; Dorothea Dix, who championed the creation of asylums (mental hospitals) so that mentally ill persons would not be held in prisons; Edgar James Elms, who founded Goodwill Industries; Fred Albee, who provided rehabilitation services at his Reconstruction Hospital to return veterans with disabilities to useful civilian life; and many others such as Harvey Wilbur, Samuel Gridley Howe, and Jeremiah Milbank (1).

At the close of the nineteenth century, government responsibility to those with disabilities began to emerge. In 1910, the first workers compensation laws were passed because of industrial injuries; the National Defense Act of 1916 created the authority to assist soldiers in reentering civilian life by providing training in agriculture or mechanical arts (2). The Smith–Hughes Act of 1917 provided states with federal funds, to create vocational education programs, and the Soldiers Rehabilitation Act of 1918 authorized the development of vocational rehabilitation to veterans with disabilities. Two years later,



the Act was extended to civilians (2). It was during these times that John Coulter, MD, established the first program in physical medicine at Northwestern University Medical School (1).

The next most significant public policy change occurred as a result of the Depression. With millions of Americans out of work, the Roosevelt Administration enacted the Social Security Act in 1935. The Act addressed the problems of unemployment, old age, poverty, and blindness. It also made vocational rehabilitation a permanent federal program (3).

World War II made a huge difference in the ways in which Americans perceived persons with disability, but also led to the formalization of physical medicine and rehabilitation as a medical specialty. Dr. Howard Kessler was a strong advocate of rehabilitation of veterans. He introduced the concept of a comprehensive medical-social-psychological-vocational approach to disability. It was during this time that Howard Rush, MD, a colonel in the U.S. Air Force, demonstrated the effectiveness of physical medicine with injured pilots. After World War II, when rehabilitation began to falter, Howard Kessler and Howard Rush persisted. The result was that the American Medical Association created a specialty board on physical medicine in 1944 (1).

The post-war expansion saw the growth of the federal government's role in rehabilitation. The Vocational Rehabilitation Amendments of 1954 forged a partnership between public and private organizations, including a federally assisted research program, and the training of professionals to staff public and private rehabilitation programs. The amendments authorized the construction of rehabilitation facilities. During this time, Mary Switzer served as the Federal Director of the Vocational Rehabilitation Department. She led the department until her retirement in 1970 (4).

During the 1960s and 1970s, there was a shift in focus from rehabilitation and disability program expansion to disability rights. Independent living, the concept of normalization, community-based rehabilitation, class action suits, and personal advocacy grew into a movement (5).

Looking back on the history of rehabilitation, we see the emergence of neurorehabilitation of persons with head injury. Howard Rush began providing neurorehabilitation to pilots injured in World War II, and he and Howard Kessler included psychosocial and psychological services as part of a comprehensive rehabilitation program. The early treatment of head injuries was also influenced by the discovery of new drugs. These psychopharmacological discoveries included lithium in 1949, chlorpromazine in 1952, the discovery of the antidepressant properties of iproniazid and imipramine in 1957 and the introduction of chlor-diazepoxide in 1960. Neuropsychiatry began to show interest in patients with neurobehavioral problems following head injury. It wasn't until the 1970s, however, that what

is looked upon as the era of "head injury rehabilitation" began.

Many efforts emerged to address the needs of persons with disability. The Rehabilitation Act of 1973 (29 U.S.C. 780, et. seq.), which focused primarily on vocational rehabilitation, also established the National Council on Disability (NCD), an independent federal agency with 15 members appointed by the president and confirmed by the Senate. The NCD later to recommend to Congress that a civil rights law be enacted that was specific to persons with disability.

The Vietnam War made its mark on the history of disability rehabilitation as better medicine and the use of medevac helicopters resulted in soldiers surviving injuries they had not in earlier times.

One of the markers of the new era in brain injury rehabilitation was the development of the Glasgow Coma Scale and the Glasgow Outcome Scale by Graham Teasdale and Bryan Jennett (Lancet, 1974, 1975). This standardized method for assessing the severity of injury and predicting long-term outcomes following traumatic brain injury helped to make improvements in acute care and pushed brain injury rehabilitation to the forefront. Sheldon Berrol, Leonard Diller, and Yehuda Ben Yishay were pioneers in innovative rehabilitation, treatment, and organized research programs. This marked the beginning of patients being referred to specialized brain injury rehabilitation centers rather than being sent to nursing homes (6). According to Mitchell Rosenthal, this paradigm shift in care of persons with TBI occurred between 1975 and 1997. Soon, for-profit rehabilitation programs sprang up, and within five years (1980–1984) the number of TBI rehabilitation programs grew from approximately 10 to 500 (6). During this same time period the continuum of care expanded substantially to include day treatment, home programs, transitional living, residential care, behavior management, life care planning, vocational rehabilitation, independent living, coma stimulation programs, and support groups. Neuropsychological assessment, cognitive rehabilitation, computers, and other electronic devices for memory, attention, and organization were used in the treatment of many of the sequelae of TBI.

In April 1980, Marilyn and Martin Spivak hosted the first meeting of what was to become the National Head Injury Foundation (NHIF) at their home in Massachusetts. The purpose of the meeting was to discuss forming an organization to serve people who had survived TBI. During that year, a Board of Directors was selected and NHIF was incorporated as a not-for-profit organization. The founding goals have relevance even to this day. The goals of the NHIF were as follows:

- To stimulate public and professional awareness of the problem of head injury—the silent epidemic.

- To make the public aware of the nature and causes of head injury and the necessary steps that need to be taken to prevent them.
- To provide a central clearinghouse for information and resources for individuals with head injury and their families.
- To provide these individuals and their families with necessary information and support during and after crisis.
- To develop a support group network for both individuals with head injury and their families.
- To establish and promote specialized head injury rehabilitation programs.
- To help educate healthcare professionals about the unique needs of individuals with head injury.
- To advocate for increased research funding and more appropriate care for individuals with brain injury.

Later, in 1983 the goal of prevention was added.

It was during this time that the consumer movement in TBI really took hold. The establishment of NHIF chapters across the country helped to fuel this movement. The NHIF moved from Massachusetts to Washington, DC, to begin a new era of expansion. Soon the name was changed to the Brain Injury Association (BIA). While BIA was expanding into research and public policy, George A. Zitnay and Martin B. Foil, Jr., founded a new international organization in 1991. The International Brain Injury Association (IBIA) rapidly grew with the support of the World Health Organization (WHO). IBIA became a leader in multidisciplinary and interdisciplinary training and treatment with the establishment of the World Congress on Brain Injury, which has since been held in Denmark, Spain, Canada, Italy, and Sweden.

During the 1980s, with the increasing interest by professionals in brain injury rehabilitation, the American Congress of Rehabilitation Medicine created the Head Injury Interdisciplinary Special Interest Group (HI-ISIG). In the late 1980s two journals, *Brain Injury* and the *Journal of Head Trauma Rehabilitation*, began publishing, greatly expanding the scientific literature in TBI (6).

The 1980s were a tumultuous time for brain injury rehabilitation. In the early part of the decade, there was a huge increase in the development of for-profit rehabilitation programs aimed at attracting the families of persons with brain injury that had insurance, court settlements, or the ability to pay. Glossy brochures were published. Recruitment techniques included flying in whole families by private jet to visit programs. Facilities looked terrific. And executives were well paid. Some call this the “golden age.” But others, particularly persons with brain injury, called it a time of shame.

In 1985, standards of care for brain injury rehabilitation were adopted by the Commission on Accreditation

of Rehabilitation Facilities (CARF). These standards resulted from the work of the HI-ISIG. A milestone in brain injury rehabilitation was reached in 1987 when the U.S. Department of Education’s National Institute on Disability and Rehabilitation Research funded five traumatic brain injury model systems of care (Thomas, 1988).

The 1980s can now be classified as a period of ups and downs, growth, investigation of fraud, decline, and then re-emergence as the decade closed with a period of downsizing, buyouts, closures, and finally settling into a period during which insurance companies questioned the value of rehabilitation and limited the amount and time for rehabilitation services. Emphasis was placed on home treatment, community-based rehabilitation, day services, independent living, and advocacy. By 2003, additional federal funding had expanded the program to include 16 participating sites throughout the United States.

In 1990, the Americans with Disabilities Act (ADA) was passed and signed into law by President George H. Bush. The Act proclaims that participation in the mainstream of daily life is the right of all Americans and calls for accommodation in housing and public spaces. The ADA was intended to foster independence and integration, affording persons with disability protection from antidiscrimination.

As important as the ADA was for antidiscrimination protection, however, it did not address many of the most pressing needs of persons with brain injury, such as assistance with access to appropriate care and rehabilitation. The ADA acknowledges that it is not so much the disability per se that makes life difficult for a person with a disability, but rather the way society responds to that disability. According to Justin Dart, the ADA seeks to change the status of people with disabilities by expecting a more enlightened attitude toward them. It rejects the long-standing and outmoded view of people with disabilities as being helpless and pitiful, and the primary role of the government as a charitable one—to take care of them through the provision of special programs and services. The ADA asserts that people with disabilities are full citizens who rightfully claim equal access and full participation, and that the role of government is to facilitate and support such claims (9).

The primary requirement of the ADA is the prohibition of discrimination. Antidiscrimination requirements for people with disabilities may be considered to have two central aspects: The first is that of not being treated in a prejudicial manner because of an individual, and often immutable, characteristic that has no bearing on the individual’s skills or capabilities. The second requires paying particular attention to the individual’s characteristics (e.g., race, sex, age or religion) to use the interaction between the individual and society to ameliorate or end the limitation or exclusion to equal access (10).

To focus greater attention on the wide spectrum of needs specific to persons with brain injury, BIA, under the direction of George A. Zitnay and with the help and support of Senator Edward Kennedy (D-MA), Senator Orrin Hatch (R-UT) and Congressman Jim Greenwood (R-PA), began work on writing the Traumatic Brain Injury (TBI) Act. Persons with brain injury provided leadership and input in the creation and passage of the TBI Act, including Sherrie Watson, Jean Ann McLaughlin, Maureen Campbell-Korves, Patsy Cannon, Gary Busey, and Marvel Vena. The TBI Act was signed into law by President Bill Clinton in 1996 (P.L. 104-166).

The TBI Act was the first federal law specifically for persons with brain injury. The law specifically established a federal grant program for states to create TBI Advisory Boards, conduct planning and assess the needs assessments of persons with TBI in order to improve access to services. The law directed the Centers of Disease Control and Prevention (CDC) to perform incidence and prevalence studies and establish educational and public awareness programs. The Act also required the National Institute of Child Health and Human Development of the federal National Institutes of Health to hold a consensus conference on the rehabilitation of persons with TBI. In 1998, an international panel of experts convened a conference, reaching a consensus that more research was needed on TBI rehabilitation.

The reauthorization of the TBI Act in 2000 (P.L. 106-310), included an expansion of the CDC's work with state registries to collect information that would help improve service delivery, expand incidence and prevalence studies to include persons of all ages as well as those in institutional settings and efforts to capture data on mild TBI. The new law also directed states to enhance "community-based service delivery systems that include timely access to comprehensive appropriate services and supports" as well as additional funding for the national Protection and Advocacy Systems to provide legal resources specifically for persons with TBI,

In 1999, the U.S. Supreme Court decision in *Olmstead v. L.C.* (527 U.S. 581), made a significant contribution to the movement toward community-based services. The court found that states are obligated under the ADA to provide appropriate settings for persons with disabilities in the "least restrictive environment." The court also found it to be discriminatory on the basis of disability for the state of Georgia to disallow the plaintiffs (persons with disabilities) to live in state-funded assisted living rather than the mental institution.

By the early part of the twenty-first century, various federal agencies were involved in brain injury research. The breadth of the federal government's commitment to furthering the science of TBI incidence and to improving rehabilitation increased. Federal efforts spanned from

prevention through education under the CDC, to biomechanics research funded by the U.S. Department of Transportation, to battlefield studies and helmet studies by the U.S. Department of Defense, to 6 bench science research centers funded by the National Institute on Neurological Disorders and Stroke at NIH, to a Cooperative Multi Clinical Trials network of 8 sites funded by the National Center on Medical Rehabilitation Research at NIH, and 16 TBI Model Systems of Care funded by the U.S. Department of Education's National Institute on Disability Rehabilitation Research.

Finally, the late 1990s and early 2000s have come to be seen as a period of cost reduction, accountability, managed care, and the closing or merging of many programs in TBI rehabilitation. Length of stay, payment, and reimbursement have become real problems. While states have sought reimbursement solutions through waivers in the federal-state Medicaid program, the Medicare program—as the largest health insurer in the nation—has not kept up with medical advances and civil rights and expectations for recovery in its reimbursements to hospitals, nursing homes, and particularly specialized brain injury facilities.

The move toward empowering persons with disabilities has led to greater expectations for quality of life and consequently, greater efforts at finding innovative rehabilitation techniques and programs. This, combined with a better understanding of how the brain can heal, has helped shape the evolution of TBI rehabilitation.

Outcomes, evidence-based practice guidelines for management of acute care, penetrating head injury, and neurobehavioral sequelae of TBI have been developed by the Neurotrauma Foundation (NTF) and the National Brain Injury Research, Treatment, and Training Foundation (NBIRTT). This is in response to the need for accountability and improvement in quality of life. Currently an international group of rehabilitation specialists under the leadership of NBIRTT is working to create a new assessment tool to measure quality of life for persons with TBI. The QOLIBRI is currently being field-tested and will soon be available for widespread distribution.

To close this historical chapter, it is important to mention that research into new pharmacological agents, stem cells, and proteomics offer new hope for improving outcomes in rehabilitation.

What is the future of rehabilitation? Traditionally, rehabilitation has been a reactive rather than proactive profession. Rehabilitation education and similar activities have been based on past experience, often with little thought given to future needs. There is agreement in rehabilitation that several issues will profoundly affect the future. Those issues include changes in the nature of work in the United States; growing diversity in the workforce;

changes in the nature of disability; advances in rehabilitation and medical technology; and alterations in the nature of strategies of service delivery.

Constant changes in rehabilitation can be predicted with certainty. History suggests that rehabilitation practitioners, especially those working in brain injury, will continue to face budget cutbacks, resulting in staffing shortages, growing caseloads and changes in the structure and function of the rehabilitation system. To respond, the field must become proactive. This will involve networking with other rehabilitation professionals, facilities, agencies and consumers. There is and will continue to be a need to deliver efficient and effective rehabilitation services that can be measured and evaluated. Finally, we must continue to provide for continuous learning and education of professionals, consumers and policy makers.” (14)

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# 3

## International Perspectives on TBI Rehabilitation

*Zeev Groswasser*  
*Ofer Keren*

### INTRODUCTION

Craniocerebral trauma has been linked historically with assault and war. Treatment of craniocerebral injuries by trephination was first described in the Edwin Smith surgical papyrus and by Hippocratic physicians. Some patients actually survived the trauma of the trephination, but most died. Over the years, the concept of cerebral compression by hemorrhage, originally described by Arabian physicians, gained recognition and eventually led to recognition of the need for decompression. Cushing (1) used meticulous debridement of penetrating brain injuries, which reduced mortality by 50 percent and resulted in a normal life expectancy for survivors. The introduction of antimicrobial and antibiotic agents, and the recognition that rapid intervention by trained neurosurgeons immensely decreased mortality from penetrating craniocerebral trauma, have both resulted in higher survival rates for patients.

Changes in lifestyle during the last century, especially the introduction of automobiles, became a major source for craniocerebral trauma. In motor vehicle accidents (MVA), brain injury is the cause of death in over 70 percent of fatal cases (2).

### THE MODERN ERA OF TBI REHABILITATION

Interest in traumatic brain injury (TBI) has risen greatly since World War II. The number of publications devoted

to what was then called “craniocerebral trauma” saw a threefold increase in the years 1956–1966 (3) and the topic has attracted increasing attention in national and international neurology and neurological surgery conferences. In the United States, the National Institute of Neurological Diseases and Blindness first designated craniocerebral trauma as a major topic of interest in October 1964. This paved the way for one of the first comprehensive conferences for the study of craniocerebral trauma that took place at the University of Chicago in 1966. The planning committee of that conference, chaired by Dr. Caveness, included neurosurgeons, neurologists, physiologists, and engineers, but no psychologists or physicians working in rehabilitation.

The translation from Russian into English of the works of A.K. Luria, *Human Brain and Psychological Processes* published in 1966 (4) and *The Working Brain*, first published in 1973, (5) led to rapid development of the field of neuropsychology, which plays a key role in the assessment and treatment of TBI patients today. In the last 20 years, TBI has become the accepted term for traumatic brain damage, and terms such as “craniocerebral trauma,” used above, have disappeared altogether from the recent literature.

In the last 150 years, the structure/function relationship has provided one of the most intriguing research topics in the neurosciences. The localistic theories that emerged from the early studies of Broca and Wernicke in

the nineteenth century were replaced in the 1930s by the holistic theory. Brain function and organization remained at center of interest, and in recent years current theories stress the dynamic aspects of brain function at the expense of the localistic or holistic approaches. The crucial role of the prefrontal cortex in human behavior has since gained increased recognition in modern neuropsychology. Historical illustrative case reports such as the case of Phineas Gage (first described in 1842) have become common knowledge (6).

Digital diagnostic brain imaging techniques introduced in the early 1970s in the form of computed tomography (CT), followed by magnetic resonance imaging (MRI), and in recent years by fMRI, PET, and SPECT have further promoted interest and research in the structure/function relationship following brain damage.

Tools developed in the field of neuropsychology have enabled a better assessment of cognitive deficits following TBI, which in turn has promoted various intervention processes designed to remedy the patients' cognitive deficits. It has become clear that the recovery processes may take longer than initially thought.

The drive to rehabilitate war veterans, probably driven by the feelings of guilt held by societies, exerted a profound effect on the rehabilitation of TBI patients. The basics of TBI rehabilitation were laid down in post-World War I Germany by K. Goldstein, who designed a center that included—in addition to the hospital—a psychology laboratory, a school, and later a vocational rehabilitation center, all for the purpose of providing comprehensive treatment (7). Goldstein evidently regarded the assessment of residual work potential and the prediction of vocational outcome as parts of the rehabilitation process (7). This type of rehabilitation approach was abolished altogether in 1933 after the Nazi takeover, especially because most of the leading physicians in these centers were Jewish. Goldstein himself left for the United States but did not pursue this line of work, described in his book *After-Effects of Brain Injuries in War*, which was published in 1942 (7). On the one hand, the state of rehabilitation in the United States at that time, and on the other hand the fact that Goldstein's main interest was aphasia and related disorders, created an atmosphere that hindered further progress along the original lines traced by Goldstein. It is noteworthy that the role of memory and attentional deficits as key sequelae influencing outcome following TBI became evident in the years after World War II.

It took almost 40 years for similar ideas regarding TBI rehabilitation to emerge, again because of war. The "Six-Day War" in 1967 and more so the "Yom Kippur War" in 1973 created the need and played the decisive role in the establishment, in December 1973, of the special medical unit devoted to TBI rehabilitation at the Loewenstein Rehabilitation Hospital (LRH) in Israel (8). TBI patients had been treated at LRH since the early

1960s. But it is worth noting that many of these patients were at that time still referred to mental hospitals because of severe behavioral deficits that may have dominated their condition.

The comprehensive model of treatment developed at LRH can be described as "Coma to Community" (Figure 3-1). It is a model of treatment that can be adopted easily by other countries. As a small country, Israel enjoys certain advantages in this respect because one center, located at the geographical center of the country, can serve the entire population. Patients with TBI had been admitted to LRH since the early 1960s, so it was a natural choice as the national center for TBI rehabilitation after the Yom Kippur War. After the war, patients with severe TBI from the civilian population, as well as victims of motor vehicle accidents (MVA) and work accidents, were referred almost exclusively to LRH. TBI patients in Israel have almost universal access to in-patient rehabilitation services. Victims of road accidents are almost always insured, while work accidents and other minor causes of TBI are covered by

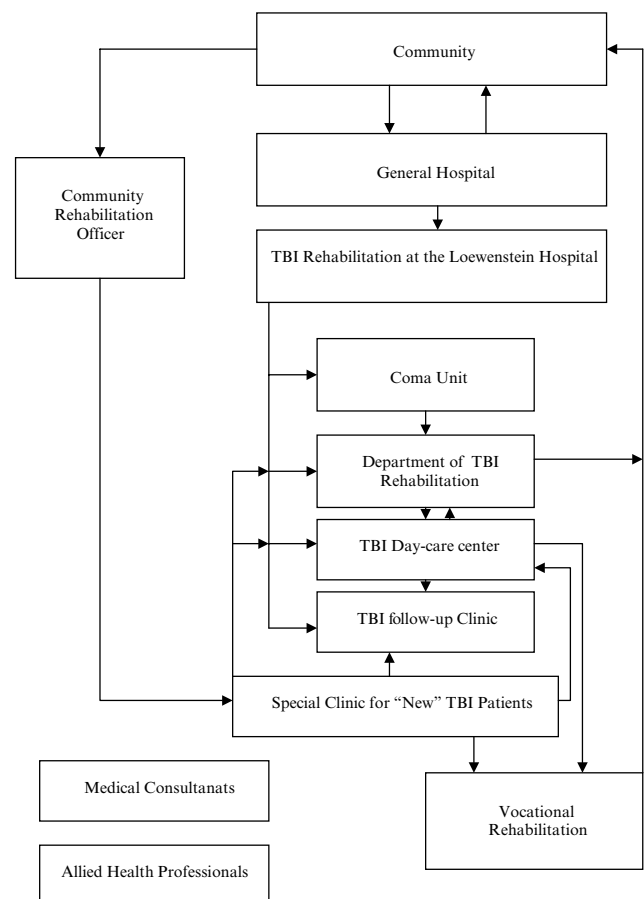


FIGURE 3-1

The LRH comprehensive "Coma to Community" TBI rehabilitation service

the “sick funds.” The establishment of a large rehabilitation center that serves almost all severe TBI patients in Israel has enabled the creation of a critical mass of knowledge regarding treatment and outcome, which was of utmost importance in the early years of modern TBI rehabilitation, before the existence of specialty conferences and journals devoted to this subject.

The LRH “Coma to Community” system provides inpatient rehabilitation facilities for about 220 severe TBI patients a year. The fact that patients are treated in a rehabilitation setting from an early stage has a beneficial effect on outcome (9–11). The out-patient program at LRH ensures continuity of care and prevents misunderstandings that often happen when patients change their place of treatment. The LRH experience suggests that large regional rehabilitation centers for TBI rehabilitation can provide a continuum of care that meets the changing needs of patients and is effective for both patients and healthcare providers. This model helps contain cost while building and maintaining trust with patients and healthcare providers alike.

### Conferences

In the early 1970s, increasing interest in TBI rehabilitation encouraged an international exchange of ideas on this topic, especially because few books or journals were devoted to the subject at that time. The Glasgow Coma Scale (GCS), first published in 1974 by Teasdale and Jennett, exerted a strong influence on research of the effects following TBI by providing a reliable score that could be used to judge the initial severity of injury (12). This made it possible to recruit large numbers of patients for outcome studies, sometimes from several centers, and to compare various methods of treatment (13–15).

Several meetings on TBI research had been organized in the 1960s in the United States, but the first meeting in Europe regarding TBI rehabilitation was organized by Prof. Ö. Höök in Oslo in 1974. Some conferences became annual meetings such as the Williamsburg Annual Meeting and the Braintree Annual Traumatic Head injury Conference. The IX World Congress of Rehabilitation International took place in Israel in 1976. As a result of the involvement of the Loewenstein Rehabilitation Hospital staff, the local scientific committee included in the program a workshop on patients with brain injury. Since then, TBI rehabilitation has become a regular part of most, if not all, international conferences in rehabilitation medicine.

The foundation by Henry H. Stonnington of the International Association for the Study of Traumatic Brain Injury (IASTBI) spearheaded both research and collegial interchange among the international brain injury community. Subsequently, George Zitnay founded the International Brain Injury Association (IBIA). Due to the efforts of Nathan Zasler, Henry Stonnington, and

George Zitnay, these two organizations eventually merged, initially with IBIA becoming the scientific arm of IASTBI. Over time, the IASTBI was simply folded into the IBIA organization, and its members were fully integrated within the latter organization. The IBIA continues to sponsor and plan a biannual international conference devoted to TBI. At these international meetings, experts as well as newcomers to the field meet each other, exchange formal and informal information, and help in the dissemination of information for the benefit of patients with TBI. In countries like the United States, it is not uncommon to have state TBI conferences performing similar functions, but on a smaller, local scale.

### Journals

Research regarding TBI developed along two main lines. The first and more established line dealt with the acute phase. This was pursued primarily by neurosurgeons caring for patients in the early phase. These researchers already had established journals where they could publish their findings. Long-term care, which developed rapidly after the 1970s, posed different questions and research problems. Some peer reviewers described these problems as being of “limited interest,” as described in editorial letters rejecting research findings and manuscripts regarding late sequelae of TBI. This situation led to the creation of special-interest groups such as IASTBI and IBIA, and also to the foundation of journals devoted entirely to TBI studies, such as *Brain Injury* and *The Journal of Head Trauma Rehabilitation*.

Recognition that the number of TBI patients in the community was growing and that rehabilitation techniques could improve a patient’s condition beyond the course of natural recovery, helped to get data regarding TBI published in more general journals in medicine and neurology. In the Editorial of the first issue of *Brain Injury*, in 1987, McKinlay and Pentland wrote: “It is a commonplace that 15 or 20 years ago there was little interest in head injury, and only a small literature addressing the acute and long-term problems it presents. Nowadays there is an extensive literature ranging through epidemiology, pathophysiology, acute management, and rehabilitation, and *Brain Injury* is an expression of that greatly increased interest” (16). Other journals that take an interest in TBI, to mention but a few, are the *Journal of Neurotrauma*, *NeuroRehabilitation*, *Neurorehabilitation & Neural Repair*, and *Neuropsychological Rehabilitation*. The number of citations relevant to traumatic brain injury between the years 1988 and 1998 was 2563 (17).

### Organizations

The increased interest in TBI, the growing number of people working in the field, and the belief that patients with



TBI present problems that are not well understood or treated by the general medical community, have created a genuine need for a “meeting place” for those involved in clinical care of these individuals. Professionals from various countries were involved in the foundation of IASTBI in the mid-1980s. As previously noted, an important role was played by the staff of the Department of Physical Medicine and Rehabilitation, Medical College of Virginia Hospital, Virginia Commonwealth University, from Richmond VA, headed by Henry H. Stonnington, who acted as the first chairperson of IASTBI and was also the first Editor-in-Chief of *Brain Injury* from 1987 to 2000. Subsequently, Jeffrey Kreutzer and Nathan Zasler were named co-editors of this journal.

### **TBI Support Groups**

#### *The Rationale for Support Groups for Post-TBI Patients*

The growing interest in TBI in the medical community, the increased number of patients surviving the acute phase, and the understanding that severe TBI patients need treatment and support far beyond the first few months post-injury, have created a need for information resources. McMorde et al. found that many patients and their families indicated that inadequate information was provided regarding important consequences of TBI such as aftercare, referral resources, and prognosis (18). Areas of greatest informational deficit included post-hospitalization resources and expectations for outcome. Clergy proved to be by far more helpful in these respects to both patients and families than psychiatrists (18).

Starting in the late 1970s and continuing into the early 1980s, the lack of resources for useful information such as books and journals, and the inadequate answers provided by the medical community, led to the foundation of support groups (SG) of patients for persons with TBI, as well as their families. These support groups were started initially by professionals treating such patients and by families of persons with TBI. The goals of such groups were to increase public awareness of the long-term impact of TBI on patients and their families, to stimulate the development of supportive services in the community, and to supply information regarding TBI (19). Peer support has been shown to be a promising approach to enhancing the coping skills of individual TBI patients and their families (20). Moreover, the impact of the cultural gap and feelings of stigma and social isolation have been shown to be universally experienced by TBI patients (21). Attentiveness, friendliness, and guidance on the part of the rehabilitation staff have been shown to have a significant positive impact on the well-being of TBI patients. Family conflicts have commonly deprived patients of familial support (21). A study of Hispanic TBI survivors demonstrated the importance of linguistic and ethnic factors in the implementation of support groups (22).

In many instances, regardless of the severity of TBI, the lives of the injured and their families are changed forever. These changes can produce a “catastrophic reaction.” (11) The impact is often devastating both emotionally and financially. Support groups can be helpful by providing useful information that in many instances may otherwise be gained only by personal experience. This is one reason that individuals trust SGs. Information about the long-term effects of the injury, about available facilities, services, and programs specializing in patients with TBI are shared by these groups. This in turn has led to the establishment of national societies. The SGs are a social reference group, exerting a positive impact on the self-esteem of both TBI patients and their caregivers. The national groups, first in the United States and then in other countries (especially in Western countries), have been able to promote changes that acknowledge the long-term medical and social needs of this special patient population.

The sociopolitical atmosphere following the Vietnam War and the growing awareness regarding both individual and patient rights laid the groundwork for the necessary changes, especially because wounded war veterans and patients with TBI were generally young and had almost normal life expectancies. Understanding that these victims needed care for life helped to promote public awareness of their needs. The fact that most patients with severe TBI had some financial support from insurance companies attracted various organizations (both for and not for profit) to start TBI rehabilitation programs, which resulted in greater availability of such programs in the United States. Almost 700 such programs existed at one time in this country. But in light of the comprehensive “Coma to Community” treatment model set at LRH in Israel, it soon became clear that many of these programs were not able to bring together the critical mass of knowledge and experience needed to provide the long-term (at times life-long) integrative therapeutic milieu needed by TBI patients, and many of these programs survived for only relatively short periods of time.

With the development of electronic means of communication, opportunities for sharing and disseminating information have increased dramatically. Numerous websites can be found today that are operated by TBI SGs, and others contain a variety of sources of information regarding various aspects of TBI. Today, the Internet plays a key role in distributing information. Entering “TBI” in any search engine returns a large number of these sites. SGs are highly developed in the United States, Canada, and the United Kingdom

Support groups quickly understood the lack of public awareness regarding the long-term impact of acquired TBI on individuals, their families, and the community as a whole. This led to consolidation of local SGs into national organizations that are able to exert greater political influence on legislation, healthcare providers such as HMOs, and the insurance industry.

*Structure of Brain Injury Support Groups* Support groups can be nonprofit or for-profit organizations. Large state or national SGs often consist of local SGs. A TBI SG can be organized in different ways, depending on the objectives and composition of its board of directors. Directors may be appointed by the families, by healthcare providers (such as rehabilitation centers and organizations), or by interested parties such as attorneys' offices. In many cases, SGs are composed of all these various sources.

A successful model seems to be one in which all three elements combine into a well-coordinated group in which professionals in TBI rehabilitation (occupational, physical, therapeutic recreational, and speech therapists; vocational counselors; physicians; nurses; and family therapists) take an active role. The activities of individual SGs differ, but they all provide information about post-hospitalization community resources for further individual and family treatment and about vocational and recreational opportunities. Some of these groups have extended their goals and are involved in programs aimed at the prevention of TBI, reducing its overall incidence. TBI survivors are involved in many educational activities of the SGs, in many instances as part of their own rehabilitation program.

*Long-term care for caregivers* Long-term cognitive and especially behavioral changes affect not only the lives of TBI patients but also the lives of those living close to them, most notably that of the caregivers (23). Studies have shown that in many cases anxiety and dissatisfaction at five years post-injury are far more severe than at about three months or one year (24–26). With time, caregivers may need more support than in the early phase, which is often disregarded or neglected by the health providers who focus mainly on treating the patient. TBI programs, however, need to assign a professional staff to provide empathetic and functional help to the patient's caregivers (27). Because this type of intervention can be done for relatively short periods of time, voluntary organizations such as TBI SGs play a key role in providing this service in the later stages of treatment.

Some SGs provide newsletters treating such important subjects as social cognition, learning, and role-modeling processes. Others provide hotlines such as the Head Injury Hotline, which is a nonprofit clearinghouse that was founded by and has been operated by head injury activists since 1985, (28) with a team of consultants that includes individuals with TBI, family members, learning specialists, nurses, paraprofessionals, lawyers, neuropsychologists, and physicians specializing in emergency medicine and neurology. They offer consultations, research assistance, case management services, legal services, and in-service training. Their clientele consists of individuals with brain injuries and their families, U.S. government officials, agency heads, educators, medical and legal professionals,

and social workers. The activities of these groups include multiple and various aspects of TBI and are open to anyone interested.

Some SGs were organized by academic institutions such as Radford University's Waldron College in southwest Virginia, enabling students to take an active role in some of the programs (29). Some SGs have established Clubhouses for survivors of TBI to serve as a bridge between the past and a healing future. For example, the nonprofit program operated by the Long Island Head Injury Association, Inc. (30) provides a place for survivors to participate in meaningful work, and an opportunity to meet and build friendships and ultimately seek gainful employment within the community. Another example is the Jodi House, aimed at providing opportunities for each person to discover new paths to regain autonomy and purposefulness within their community (31).

Virtual support has also been developing in the last years. Examples of such activity can be found at the website of the TBI chat room ([www.tbichat.org](http://www.tbichat.org)) which had an impressive increase of its use from 135,552 visits in 1998 to 554,244 in 2002. Such SGs help those who would enjoy attending SG meetings but are unable to do so because of problems of transportation or distance. A TBI survivor can contact the chat page 24 hours a day, participate in the general chat room, or enter one of several specialized chat rooms such as TBI in children. A chat room has been designed for children with TBI who are under age 17 years, as well as, their care providers and family members (32).

Today the Internet plays a key role in distributing information about resources regarding TBI rehabilitation. SGs have developed as a result of the understanding that patients and their caregivers require prolonged care, beyond what the health care systems and insurance can provide because of financial and knowledge barriers. Unfortunately, these groups are well developed and active only in countries in which rehabilitation medicine has become part and parcel of the routine medical service. It is hoped that other countries will soon recognize the special needs of TBI patients and provide for them. SGs can be instructive in bringing about this much needed change.

## CONCLUDING REMARKS

The understanding and treatment of patients with traumatic brain injury has changed greatly in the last 35 years. As more patients survive the very acute phase and are referred to rehabilitation, the demand for rehabilitation services has been on the rise. Furthermore, recognition that these patients may need treatment and support for the rest of their lives increases the demand for rehabilitation services all over the world. Rational use of resources is a must, and the rapid dissemination of "how-to-do" information

can promote the creation and improvement of TBI rehabilitation services for these individuals and their families, as well as society at large.

The established SGs and the national and international societies devoted to research and treatment of TBI, mostly active in Western countries, should become a source of inspiration for expanding services to these patients elsewhere in the world. Rehabilitation medicine is still one of the branches of medicine to which only a fraction of the people who need it have access. TBI rehabilitation, being more complex and expensive due to the large team needed for comprehensive treatment explains why in many countries these services are in their infancy. Today “how-to” data is becoming increasingly available, but communities and countries have to consider a different allocation of resources to properly implement TBI rehabilitation programs including prevention. Established TBI rehabilitation services are also under considerable financial pressure, which can promote research into more cost-effective prevention as well as treatment solutions. International cooperation in research will be essential in the coming years to achieve an evidence-based foundation for the practice of TBI rehabilitation. Ultimately our goal should be to provide cost-effective treatment that improves outcome, as well as, quality of life.

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# 4

## Training and Certification of Care Providers for Persons Sustaining TBI

*Margaret A. Turk  
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### BACKGROUND

An increasing number of individuals have survived traumatic brain injury (TBI) as a result of advances in medical technology, emergency medical procedures, and neurosurgical techniques (1–3). An estimated 5.3 million Americans currently live with disabilities resulting from brain injury. This means that over 2 percent of the American population is living with disabilities caused by TBI (4). Estimates indicate that one million people are treated for head injuries and released from hospitals across the country each year, resulting in 80,000 people experiencing long-term disabilities. TBI is one of the most common childhood injuries (5).

TBI can significantly affect many physical, cognitive, and psychological processes, significantly disrupting the lives of individuals who experience such injuries. Survivors and their families require varying degrees of support along a continuum of disability. Early needs are usually met within the emergency department and/or acute care hospitalization, followed by acute rehabilitation. Medical and health professionals are the primary providers of service, interacting daily with patient and their families. Rehabilitation services are multidisciplinary, and the goals of care and service are restorative. Specialized programs and providers are sought to deliver quality care. Subacute and longer-term post-acute care needs may be very high, and may not always require health professionals. The services

often are provided by different agencies and multiple health professionals, making coordination and continuity of services difficult. Post-acute care often focuses on behavioral plans, daily structure, and developing creative typical tasks. Support aides require communication skills and at least a knowledge base of behavior modification. With an increasing numbers of survivors, there is a greater need for trained and experienced providers for the acute through post-acute continuum.

Families are usually unprepared for their family member's injury, hospital course, and long-term rehabilitation. Changes in the family member are difficult to understand and difficult to deal with, despite educational efforts through rehabilitation programs. Often, these changes have a negative impact on families who then often become the primary caregivers after discharge from the hospital or acute rehabilitation programs (6, 7). Family caregivers of persons with brain injuries report high levels of depression and difficulties coping with the sequelae of brain injury (8–10). Family members are particularly challenged by the altered personalities and behavior changes exhibited by their loved ones (11).

Families may have to adjust their employment and social schedules in order to provide the level of care necessary for their family member with TBI. This may lead to feelings of social isolation, financial burden, and increased levels of stress. Employers, friends, and even family members may not believe that the individual has

sustained a disability, thereby undermining the support necessary to assist him or her in adapting to life with a disability (2). Return to work and other previously held social roles might not be possible following injury, contributing to further disruption and stress within the family. Osberg and colleagues (12) suggest that with the necessary systems of support, family members can avoid some of the psychosocial problems that arise from caring for a family member with TBI.

Clinical practice, programs, and research in traumatic brain injury medicine have grown significantly over the past 35 years. Persons with TBI and their families, however, have reported the service system is “unorganized, uneducated, unresponsive, and uncaring.” (13) A parent of a child with brain injury writes, “Another area of concern is the insufficient numbers of caregivers with training in ways brain injury differs from other neurologically impairing conditions. . . . Until caregivers better understand the cognitive and behavioral changes and learn more effective methods of dealing with deficits resulting from injury to the brain, we’ll still be where we are today” (14). On a national and more general level, the Institute of Medicine (IOM) report, “To Err Is Human: Building a Safer Health System,” notes the importance of communication among multiple providers and the need for standards for training and certification especially regarding safety and prevention of medical errors. At present, however, there exists no formal training or certification for medical health care providers within the field of brain injury medicine. Only recently has there been certification of brain injury care providers, those providing post-acute care within the community.

This chapter will review the state of the field regarding accreditation for programs, as well as training and certification of health care professionals and paraprofessionals providing front-line care and support in the community.

## PROGRAM REVIEW AND ACCREDITATION

An initial attempt at standardizing rehabilitation care and assuring quality care was program evaluation and accreditation through the Commission on Accreditation of Rehabilitation Facilities (CARF). CARF was established in 1966 to ensure quality services for persons with disabilities and others receiving rehabilitation services. Improved safety, value, and quality of care of persons receiving services are a part of their mission. It is an international nonprofit accrediting body that accredits providers for specific services (e.g. behavioral health, employment and community services, medical rehabilitation). CARF standards are developed through leadership panels, advisory committees, focus groups, and field reviews. Persons served are also involved in the development of CARF standards.

The standards for brain injury programs were first offered in 1985, focusing on inpatient rehabilitation programs. Outpatient programs standards for accreditation were obtainable in 1988. Presently, there are standards for a variety of brain injury program services, beginning with inpatient rehabilitation at multiple levels and transitioning to residential and/or vocational services. CARF accredited programs serving persons who have sustained brain injury include over 100 inpatient rehabilitation programs, about 140 outpatient programs, more than 300 residential programs, almost 50 community services programs, and more than 70 vocational programs. Standards cover adult programs and programs for children and youth.

CARF has been responsive to the changing service needs over the last 25 years. As new services developed in the field, the Board of Directors has supported development of new standards. Standards are reviewed and updated on a routine basis. Program standards specifically for brain injury programs have provided some semblance of consistency for certain program elements, and are an initial step in assuring high quality care for persons who have sustained brain injuries.

## MEDICAL AND HEALTH PROFESSIONAL CARE PROVIDERS

Brain injury rehabilitation has been provided for over 35 years in the United States, initially as a part of a larger rehabilitation program, and, increasingly since about the 1980’s, as dedicated programs. Service provision has moved beyond hospitals and clinics, and into residences and communities. Advancements of medical science and vast improvements in medical and surgical care have presaged the growth of knowledge and practice. Patients often require the services of an interdisciplinary treatment team consisting of physicians, physical therapists, occupational therapists, speech language pathologists, rehabilitation counselors, psychologists, and social workers among other professional and paraprofessional staff. Interdisciplinary rehabilitation team members are typically guided by a set of standards of ethical practice for their particular professions (15). Physicians and health care professionals have risen to the challenge to provide high quality care, although subspecialization within disciplines has been acknowledged by acclamation and not certification.

Health professionals require standard training and licensure. Requirements of education and training regarding traumatic brain injury within each discipline now exist, although implementation may be uneven. Health professionals often gain experience by sharing information through team interactions, mentorship, or courses. Training and licensure for professionals does not require specialization in the care of persons who have sustained brain injury. There are no certification programs for

specialization in the care of persons with brain injuries. Most disciplines do not have certification, but rather special interest groups in professional organizations (e.g. speech and language pathology). And where there may be special certification or plans for certification (e.g. physical therapy, psychology, occupational therapy), it is not specific to brain injury medicine or rehabilitation, but to a more general rehabilitation or components of a TBI service need.

The need for training and certification has been recognized increasingly nationally and internationally (16–19). The need to protect the public has been highlighted through the IOM report. The American Board of Medical Specialties (ABMS) has acknowledged this responsibility, and subsequently enacted implementation requirements of each member Board. These require programs of Maintenance of Certification within all represented specialties, and that subspecialty certification be reviewed through a vetted process.

There is a trend to formalize physician training in the management of persons who sustain brain injury. Physical Medicine & Rehabilitation (PM&R) residency programs developed formal training in Brain Injury Medicine during the 1980s and 1990s. A questionnaire survey report of PM&R residents and program directors conducted in 1991 concluded that two-thirds of programs either offer a formal rotation or require residents to participate in a clinical rotation in brain injury medicine (20). The findings of this and other surveys supported a need for more training in brain injury medicine for residents, including additional training sites across the continuum of care (19, 20). Bell and Massagli (19) reported that PM&R residents endorsed the position that a rotation in a skilled nursing unit providing services for individuals with brain injury offered unique clinical experiences. Currently, all PM&R residents must have formal training and competency in brain injury medicine, which is mandated through the Accreditation Council on Graduate Medical Education (ACGME) program requirements. Basic requirements for certification in PM&R include successful completion of an ACGME approved residency in addition to passing written and oral American Board of Physical Medicine & Rehabilitation (ABPMR) examinations. Because PM&R training and examinations require substantive coverage of brain injury medicine, certification in PM&R conveys a basic competence in brain injury medicine (BIM).

Beyond basic competency, there also exist formal (but not ACGME approved) Brain Injury Medicine Fellowships in PM&R. These fellowships and advanced clinical experience at academic and brain injury treatment centers provide the underpinnings for further expertise in BIM. The Brain Injury Special Interest Group (BISIG) of the American Academy of Physical Medicine & Rehabilitation (AAPM&R) supports these efforts. The BISIG

organized the development and writing of curricular materials for brain injury medicine fellowship programs. This material has been utilized by fellowship training program directors and mentors to provide structure and didactic content to fellowship training programs in existence or under development. The document has been updated, most recently in 2003.

Beyond PM&R, a number of other specialties engage in elements of brain injury medicine. Foremost among these are neurology and neurosurgery. These programs are most frequently focused on the immediate acute issues or subsequent co-morbidities (e.g. seizures, increased intracranial pressure). The clinical experience in post acute brain injury medicine is not required. Although some programs support this experience, the focus and intensity is widely variable. In general, the route to significant clinical participation in post acute Brain Injury Medicine is through fellowships, a limited number of which exist. These fellowships are not ACGME approved, nor is training sanctioned by their specialty Boards. Post residency training for neurologists is available in a number of fellowships providing clinical management and diagnostic experience across a variety of neurological diagnoses along with the associated therapy interventions.

None of the aforementioned fellowship programs are accredited through ACGME and there is no formal subspecialty certification in Brain Injury Medicine through ABMS. Therefore physicians who have completed the additional year of study are not formally certified by any ABMS Board.

The American Board of Physical Medicine and Rehabilitation is developing a Brain Injury Medicine subspecialty proposal for ABMS approval. The rationale for establishing this subspecialization is:

- To provide core competency standards of training for the evaluation and treatment of patients with brain injuries;
- To provide a high level of care for patients with acquired brain injury and their families in hospital and outpatient settings, and over the continuum of the process of recovery;
- To provide physicians with brain injury medicine administrative skills for activities such as program development, quality assurance, facilities planning, standards-setting;
- To promote and strengthen research for the advancement of the clinical science of brain injury medicine, including prevention, treatment, and restoration of function and outcomes research;
- To increase the number of expert clinicians, teachers, and investigators dedicated to the care of survivors of brain injury.
- To recognize physicians who have successfully completed additional training in brain injury medicine

programs beyond the primary residency training education in psychiatry or neurology.

- To improve education in brain injury medicine for residents in psychiatry and neurology, residents in other training programs, medical students, practicing physicians, and other medical personnel.
- To generate academic interest in the psychiatric and neurological professional societies.

The formal process requires discussion and vetting through ABMS. The intention of ABPMR is to have an inclusive process with an opportunity for all physicians practicing Brain Injury Medicine to have access to the certification process.

There are many disciplines involved in the ongoing care, medical management, and rehabilitation of persons who have sustained brain injury. Although there are expert clinicians in the field, there is no formal certification for any of the professionals involved. Consumers and their families have made a strong case for the requirement of well trained and certified health care providers in the field of brain injury medicine.

### **COMMUNITY CARERS AND PARAPROFESSIONALS**

Following discharge from the acute or sub-acute setting into the community, many persons with brain injury require ongoing care. Brain injury is a lifelong injury that impacts function across the lifespan. Support needs are typically very high, although social networks generally consist of only family members and service providers (13). Oftentimes, persons with brain injury continue to require the services of a multidisciplinary treatment team. Unfortunately, these services are often spread among several different provider agencies, making coordination and continuity of service a management nightmare.

Unlike the pre-existing community services for persons with mental illness or developmental disabilities, developed in the 1970s as part of deinstitutionalization, community services for persons with brain injury are relatively new. Further, attempts to “fit” persons with brain injury into pre-existing community service models (i.e. those for persons with developmental disabilities or mental illness) have attained limited success toward meeting the needs of persons with TBI. These factors contribute to the serious need for specialized training to meet the various needs of persons with brain injuries, caregivers, and their families.

Post-acute community based brain injury rehabilitation is not only a relatively new field, but is also impacted upon by misconceptions, cultural diversity, and inaccurate knowledge about TBI among community service providers. Many of the individuals who live in the

community today would have likely not survived their injuries 25 years ago (16). The developments in emergency medical procedures, medical technology, and neurosurgical techniques, have sustained the lives of persons with brain injury, as the community services available for them are being established.

There is limited literature discussing the need for formalized training of providers of TBI services. However, the literature that is available speaks to the need for specialized provider training. The individuals who provide care to persons with TBI residing in the community are most often family members and direct care staff. Paid helpers can often lessen the stress placed upon family members, assuming the paid helper understands the nature of the injury and its sequelae.

Research on paid care work as it applies to persons with brain injury is virtually absent from the literature. McCluskey (21) found that agencies needed to increase efforts to train and orient new staff to the types of challenges they would face working with persons with brain injury. She also suggested that persons with brain injuries would benefit from closer contact between professionals and paid caregivers. Given the restrictions funding sources impose on treatment programs for persons with brain injuries there may be limited opportunities for professional intervention, placing greater emphasis on the importance of training care givers to implement activities to improve the functional performance of persons with brain injury (22).

The specific educational need areas that have been identified include several areas integral to the provision of rehabilitation services to persons with brain injury including; treatment of cognitive deficits, family and social issues, behavior modification techniques, and adjustment to brain injury (16, 18). The literature has also differentiated between the types of training and knowledge required by professionals and paraprofessionals and those with direct versus less direct care of the person with brain injury.

A demonstration project through the New York State Department of Health responded to the need for education of care providers and support for this difficult to serve population. Experts in the field of brain injury rehabilitation developed support for persons with brain injury, family members, friends, and community support staff. Additionally, the program offers an “apprentice” aspect that allows caregivers to receive intensive, contextualized training and coaching, enabling them to better serve persons with brain injury. The results of a preliminary cost-effectiveness study of the program (23) suggest that community supports for persons with behavioral issues resulting from TBI can be provided in a cost-effective manner, although recommendations are made for a systematic analysis of quality of life indicators before broader policies and programs are established.

The lifelong sequelae of TBI often exhaust private insurance funding streams early in the rehabilitation process. Therefore, public programs such as Medicaid and Medicare often become the primary sources of payment. Several states have established waiver programs for persons with TBI. These programs offer opportunities for designing integrated service plans for individuals with brain injury who would otherwise require some type of inpatient care. Care needs usually include support for specialists in case coordination and behavior management, not otherwise funded through typical private insurance. New York State's TBI Waiver Program offers long-term support focusing on post-rehabilitative care. The services offered by the waiver program are fashioned to offset several of TBI's sequelae. The services include: Service coordination, home and community support services, non-medical transportation, specialized medical equipment and supplies, home modifications, intensive behavioral supports, community integration counseling, substance abuse counseling, day programs, and independent living skills training. The services are based in a philosophy of individual choice, while accounting for the accompanying realities of needs, health and welfare issues, and budgets. One of the major challenges faced by provider agencies across the state has been the difficulty to attract and retain qualified staff. This may be a result of the lack of understanding of the behavioral and psychosocial sequelae associated with brain injury.

### **American Academy of Certified Brain Injury Specialists**

A 1990 survey of 565 acute, subacute, and post-acute programs regarding the training needs of licensed and non-licensed staff brain injury services noted that seventy-five percent of the respondents (45 percent response rate) indicated that specialized training is needed for licensed staff, and 84 percent indicated that training is needed for non-licensed staff. This was further supported by Becker (18) who reported that respondents to their survey about education and training needs for staff endorsed specialized training for paraprofessionals, even more than for professionals.

As a result, the Brain Injury Association of America established the American Academy of Certified Brain Injury Specialists (AACBIS) as a standing committee of the association to address training needs. AACBIS operates under its own by-laws as approved by the Board of Directors of the Brain Injury Association of America. AACBIS Committee members are experienced professionals in the field of brain injury rehabilitation who volunteer their time and expertise to developing a certification program that meets the needs of the brain injury community. AACBIS currently offers certification for Brain Injury Specialists. The program is governed by

AACBIS and is administered by the Brain Injury Association of America in McLean, Virginia.

In 1996, AACBIS was established to assure the highest possible standards of rehabilitation and care for persons with brain injuries. The AACBIS is the only organization offering specialized training and certification programs for care givers of persons with brain injuries. AACBIS offers national certification programs improving the quality of care through the establishment of best practices for the education and training of individuals working in the field of brain injury services. The AACBIS offers a voluntary national certification program for both entry-level staff and experienced professionals working in brain injury services. AACBIS provides staff and professionals the opportunity to learn important information about brain injury, to demonstrate their learning in a written examination, and to earn a nationally recognized credential. Since its inception the program has certified more than 520 professionals. The AACBIS certification program is specially designed to address specific training issues in brain injury services and complement other credentials.

The AACBIS program is divided into three levels: Certified Brain Injury Specialist (CBIS)—Basic, CBIS—Instructor, and CBIS—Examiner. The curriculum includes units in the following areas:

- Brain Behavior Relationships
- Functional Impact of Brain Injury
- Health and Medical Issues
- Philosophy of Treatment
- Children and Adolescents with Brain Injury
- Brain Injury: A Family Perspective
- Legal and Ethical Issues

Critics of the examination focus on it being knowledge based when many of the skills integral for effective work with this population rely upon technique. Carnevale (24) developed a model that was both knowledge and practice based. The model utilized a mobile team approach, educating caregivers and persons with brain injury on how to implement and sustain home-based behavior management programs. The natural environment (e.g. home, community) brought to light the importance of flexible interventions that addressed both client and care giver needs. Training programs should focus on the "real life" or functional impact that brain injury has on an individual. Ideally, trainers could incorporate a model that includes visiting the settings in which the care giving is taking place or at least viewing videotapes of every day interactions between the person with the TBI and his/her environment. In short, at least a portion of training must be contextualized to increase the likelihood of positive impact given the cognitive and behavioral sequelae of TBI. Training programs specifically fashioned



to provide knowledge and skills training regarding brain injury are needed to facilitate both the caregiver's and the person with brain injury's adjustment to providing/receiving services.

### SUMMARY

With advancements in research and science, there have been improvements in acute and emergency medical care, with a significant increase in the numbers of persons who survive brain injury. Residual impairments from the brain injury include a variety of conditions, however cognitive impairments are often the most difficult to manage. Health professionals with expertise in brain injury medicine are required to provide ongoing services and support. Consumers and professionals recognize the importance of subspecialty training and certification.

Program accreditation has provided a base for delivery of quality services at a systems level. Individuals providing those services should also receive appropriate training, and ultimately certification, to further assure high quality care and avoidance of medical errors. The establishment of the American Academy for the Certification of Brain Injury Specialists (AACBIS) is a dynamic step toward addressing the needs and concerns of the brain injury community. Subspecialty training and certification in brain injury medicine and rehabilitation should be considered across all disciplines serving the needs of persons with brain injury. Programs offering such training narrow the information gap between healthcare professionals in the tertiary care hospitals and those in the long-term care facilities, contributing to the integration of brain injury services across the continuum of care. Partnerships among professional organizations, credentialing bodies, service agencies, and accrediting bodies must be forged in order to further integration of knowledge and skill sets into community based brain injury services.

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# 5

## Conducting Research in TBI: Current Concepts and Issues

*Amy K. Wagner*

### INTRODUCTION

The National Center for Injury Prevention and Control suggests that injuries have a substantial impact on the lives of individual Americans, their families, and society. The consequences of injuries can be extensive and wide ranging. They are physical, emotional, and financial; in the case of disabling injuries, the consequences are enduring (1). TBI is no exception to these consequences. TBI is an epidemic in the United States with an overall incidence of 200 per 100,000 per year (2). It has been well established that TBI causes chronic debilitation and functional loss over a lifetime. Unlike other disease processes with later onset, survivors of TBI often have many decades of productive life loss, costing themselves, their families, and society much with loss of the capability for competitive employment and other meaningful community roles. An estimated 5.3 million Americans, or 2 percent of the population, currently live with disabilities resulting from brain injury, and the national cost to society is estimated to be \$48.3 billion per year (3). Injury is the leading cause of years of potential life lost before age 65, and TBI is responsible for a greater proportion of this mortality rate than most other types of injury (1). For survivors, TBI often results in disturbances of cognitive, behavioral, emotional, & physical functioning. Impairments within these domains can be a persistent & debilitating problem. Mild TBI is often

undiagnosed, making the public health burden even larger than reported estimates indicate.

The magnitude of TBI related public health burden mandates that TBI researchers delineate the contributing mechanisms of injury and recovery, evaluate and implement effective treatments, and accurately prognosticate outcome with effective assessment tools. In the population with TBI, patients can have markedly different outcomes, despite similarities in the extent of the initial insult and in type of clinical management. Additionally, the population sustaining TBI is diverse, and a broad and complex range of internal and external factors can influence injury and recovery. These factors make accurate prognostication, sensitive outcome assessment, and effective conduct of clinical trials challenging issues in TBI research. To date, there is a paucity of proven interventions shown to significantly reduce morbidity and mortality or improve recovery and quality of life. Mechanisms of injury, neuroplasticity, and recovery are not fully understood, and outcome prognostication unrefined. In this chapter we discuss unique issues with conducting research in the population with TBI and appropriate outcome assessment in this population. We also highlight the importance of translational research and preclinical trials, evaluate challenges and pitfalls with conducting clinical trial research in this population, and outline issues with statistical approach and research design. Finally, we will discuss future considerations and pioneering directions for the field of TBI research.

### **Unique Aspects Associated with TBI Research**

TBI is a complex disease involving both primary (focal and diffuse injuries) and secondary injury, with secondary injury involving complex biochemical cascades that lead to excitotoxicity (4–6), brain swelling (7), loss of cerebral blood flow autoregulation (8), oxidative injury (9, 10), inflammation (11, 12), and cellular necrosis and apoptosis (13, 14). Overlaid on this complex myriad of pathophysiological cascades are the influences of genetic make-up, and other premorbid and demographic characteristics that can influence the extent of injury or recovery. For instance, genetic polymorphisms associated with APOE have linked ApoE-4 expression to outcome after TBI (15–17). Other factors such as age, gender, minority status, and previous education may also impact outcome (18–21). Further, there is variability in the type and intensity of both acute and rehabilitation care that patients may receive. These factors are often influenced by treatment location, social supports, and source of payment (22–24). The multidisciplinary approach to therapies also provides unique challenges in understanding what portions of the rehabilitation process are crucial in improving a particular individual's recovery course. All of the differences in injury variables, personal characteristics, and treatments outlined above can create variability in recovery from TBI. This variability creates unique challenges for researcher in TBI to tease out the important mechanisms associate with injury and recovery, identify appropriate and effective therapeutic targets, and accurately prognosticate outcome.

### **Researching the Population with TBI**

Researching the population with TBI poses other unique methodological challenges to researchers regarding recruitment, population characteristics and follow-up. Biases with recruitment may introduce systematic bias into the study population. One study evaluated this issue in mild TBI by comparing demographic, premorbid, and injury related characteristics of their population. Those who had more severe injuries, who were hospitalized, and who had a significant additional major injury were more likely to consent to participate in the study (25). In studies requiring the evaluation of patients who are unable to consent themselves for enrollment in a research study and/or the immediate implementation of a treatment intervention, obtaining consent can be a challenging issue that impacts recruitment and study design. Recently, one multicenter trial investigated the efficacy of early hypothermia treatment implemented within the first six hours from injury for patients with severe TBI. At the beginning of the study, informed consent was required for each study patient. During the course of the study, federal regulations changed

to allow waived informed consent. Post-hoc analysis of this study population showed that with waived informed consent, time to randomization and treatment implementation decreased, patient accrual increased, and minority representation in the study population increased (26). This analysis illustrates the potential importance of waived informed consent on the integrity of early treatment interventions and in minimizing recruitment bias.

Alternatively, systematic bias may be introduced into a clinical data set through loss to follow-up. Loss to follow-up is an inherent problem when conducting research in the population with TBI. One study evaluating loss to follow-up using a variety of data sets, including a single center, multicenter, and statewide surveillance data set, found a loss to follow-up rate of approximately 37 percent and 58 percent one year and two years after injury respectively. Additionally, there appeared to be a selective bias to lose those who were socioeconomically disadvantaged, with violent etiologies of injury, and with a history of substance abuse (27). Systematic bias with loss to follow-up can significantly decrease the generalizability of study findings and potentially confound apparent treatment efficacy with clinical trials.

A myriad of variables, including patient comorbidities and complications (28, 29), gender (18, 30, 31), cognitive reserve (32), injury severity (18, 32, 33), injury type (34–37) minority status (38), social supports (39) and acute discharge location (24) may all influence outcome. Additionally, patient recovery can occur over a prolonged period (40–42), and outcome assessment may vary with the type of individual (patient, caregiver, clinician) interviewed (43). Each of these issues must be considered carefully when designing studies. The appropriate use of covariate analysis, including time variables for longitudinal studies, and stratification is often necessary to avoid confounders obscuring research results. Time post injury is also an important consideration when designing clinical trials to minimize the effects of natural recovery on the apparent treatment effect.

### **Outcome Assessment Tools in TBI Research**

The World Health Organization (WHO) has provided widely accepted definitions of impairment, disability, and handicap that have resulted in a conceptual framework by which world wide research has been conducted investigating the impact of injury and illness on individual function (44). This system more recently has been replaced by the International Classification of Functioning, Disability and Health (ICF) (45), providing an updated framework for rehabilitation research (46). Several existing TBI assessments measure outcome within more than one of these domains. Commonly utilized TBI outcome assessments vary in scope and mode of measurement. Some outcome assessments are general and

designed to provide a global index of outcome, [e.g. Glasgow Outcome Scale-extended (GOS-E) (47), Disability Rating Scale (DRS) (48)]. Others are meant to measure functional abilities for daily activities [Functional Independence Measure (FIM) (49)] or community integration [Community Integration Questionnaire (CIQ) (50, 51)]. Assessments may also focus on quality of life (42, 52, 53), caregiver needs (54, 55), while others focus specifically on neuropsychological performance (41) or psychiatric dysfunction (56, 57). Finally, measurement tools may target specific populations, such as those with mild TBI (58). In particular, outcomes assessment is an important aspect of TBI rehabilitation research. However, studies often published in rehabilitation journals do not report the validity and reliability of the outcome measures used (59). Variable definitions and operationalization as well as associated social values and target population can be difficult to address when developing new or utilizing existing TBI outcomes assessments (60).

Multimodal assessments are often necessary to effectively reflect the complex range of factors affecting TBI outcome. However, no single measurement tool can encompass all relevant areas of TBI outcome. Additionally, there are limitations with the collection and analysis of many existing measurements. There are ceiling effects associated with some measures as individuals with TBI improve over time (61), and some outcome measures have a limited ability to measure group differences in function over long evaluation intervals (62). Attention to cultural, minority, age and gender related differences in response range for outcome assessments should also be considered when selecting assessments and interpreting results (19, 63–66). Choosing an appropriate primary outcome measure is of critical importance when designing clinical trials, selecting a proposed treatment effect size, and for developing effective models for prognostication. Appropriate and well validated outcome measures are often most effective when they target a population with a varied demographic profile and broad range of injury severity, are able to accurately place subjects in appropriate outcome categories at given time intervals, and are sensitive to change over time. Additionally good outcome assessments often link impairments to disability to handicap. For clinical trials, the GOS-E has gained popularity as a primary outcome assessment tool and is thought to be more sensitive than the standard GOS (47). However, The Functional Status Examination (FSE) is a well-validated new instrument that has been utilized in long-term studies for the population with moderate and severe TBI (42, 67). Its measurement properties are linked with other constructs such as family burden, depression, and satisfaction with functioning that make it an effective multi-modal assessment (42) that should also be considered when designing clinical studies.

Researchers should also examine prospective outcome assessments they plan to use to determine if appropriate steps have taken previously to validate that measure in their population of interest. Mode of assessment administration presents some unique concern regarding the validity of the assessment tool chosen. Some measures, including FIM (68) and CIQ (51) have been validated for administration over the telephone, however, many other measures have not been formally validated for multiple modes of administration, despite their widespread use in this manner. Telephone and mailings result in the study population becoming an unseen entity, which can introduce variability and bias into the responses generated.

Cognitive impairments of persons with TBI often make the use of proxies for outcome assessment and evaluation attractive. However, self-awareness of deficits for people with TBI (69) and participant-proxy differences in disability perceptions and quality of life (70) may preclude participant-proxy responses from being interchangeable. Some measures have been specifically evaluated for their reliability and accuracy when administered to both individuals with TBI and their proxies (68, 71), while others have not been evaluated for participant-proxy agreement. Recently, the intraclass correlations between participants with TBI and participant selected proxies on the Craig Handicap Assessment and Reporting Technique (CHART), the CIQ, and the FIM were evaluated. Results showed a high intraclass correlation for participants and proxies, with the highest values occurring on items assessing concrete or observable information (72). Other studies in a variety of patient populations also indicate that patient proxy agreement is generally better for questions regarding physical dimensions of functional status, and agreement is less consistent for questions regarding subjective or affective aspects of outcome assessment (70). Investigators should take time to carefully consider their primary outcome measure and choose their criteria for considering persons with TBI to be a capable respondent. The agreement between patient and proxy responses should be evaluated prior to an outcome assessment's inclusion in a study in order to avoid over or under estimation of treatment effects or invalid conclusions. Further, consistent criteria for the selection of a knowledgeable caregiver or significant other should be considered in the research design.

### Clinical Trials in TBI

Randomized clinical trials are the gold standard by which researchers in any field of medicine test the efficacy and safety of treatment interventions. Clinical trials, particularly randomized clinical trials, provide a strong foundation for evidence based clinical practice and justification of payors to reimburse for treatments and therapies (73). However, in the area of TBI, there have been few clinical trials that have definitively identified any effective

treatments for reducing morbidity or improving recovery. Numerous TBI clinical trials of acute pharmacological interventions, intended to improve functional & neuropsychological outcomes, have been conducted over the last 25 years, with often disappointing results (2, 74–80). The justification for virtually all of these trials were positive findings in animal studies, using rodent models, testing the trial drug or intervention that could not capture variables that may influence treatment outcome, such as, gender, age, and genetic variability (81, 82). As mentioned above, TBI is a heterogeneous disease, with a multitude of secondary injury cascades, affecting a diverse population. The complexity of the disease and diversity of the population it affects makes designing clinical trials in TBI particularly challenging.

For TBI rehabilitation research, double blind randomized control trials are particularly difficult to carry out. Sample sizes tend to be small, and the number of confounding variables are often quite high. There is a lack of consensus on appropriate outcome measures or how to objectively quantify rehabilitation based interventions, and (unlike acute care trials) post-intervention improvements may not be seen for months or years. Rehabilitation research also focuses on the improvement of functional abilities, participation in the community, and quality of life (46). For instance, social interventions such as caregiver education may improve community integration and quality of life for the population with TBI. Rehabilitation outcome often can be considered context specific and affected by a patient's physical environment, social environment, and personal attitudes and expectations (83). Contextual factors may influence rehabilitation outcome and decrease the generalizability of clinical study results. Despite these challenges, some high quality rehabilitation based randomized clinical trials have occurred in the areas of seizure prophylaxis (84, 85), community based rehabilitation for long term survivors of TBI (86), Methylphenidate treatment (87), and cognitive rehabilitation (88). However, replication studies, studies with large population numbers, and the generalizability of findings to a large population are difficult to find in any area of TBI rehabilitation research.

A recent analysis regarding clinical trials in rehabilitation (89) suggests that characterizing participants in rehabilitation research studies is of critical importance to eliminate confounding, to ensure comparability across treatment conditions, and to adjust for differences in prognosis among participants. Additionally, the treatment or intervention must be adequately and objectively characterized in terms of mechanism of action, dose, route, intensity, and subject participation. Outcome measures utilized for characterizing treatment efficacy need to be sensitive and appropriate. Investigators should identify the appropriate target of their outcome assessment (e.g. disease, impairment, activity, participation, quality of life) and

ensure the measureability of their outcome target with the treatment intervention. Often, broadly defined outcomes such as quality of life have several factors that impact it. As such, a single intervention may impact specific impairments after TBI, but those changes may not be large enough to translate into a meaningful change in quality of life (89). Additional challenges in rehabilitation research occurs with blinding of physical treatments and with limitations of crossover designs when significant contamination of the study population from cross-training might dilute the effectiveness of the treatment intervention (90).

Multicenter clinical trials in TBI are considered necessary since the ability of a single center to recruit enough subjects to provide adequate statistical power is often limited. However, several statistical and design issues have been identified by investigators directing multi-center clinical trials that begin during emergency and intensive care. Intercenter variance in patient care and adherence to the research protocol has been a fatally flaw in some recent multicenter clinical trials. For example, it has been reported that intercenter variation, not explicable by injury severity or type, was responsible for approximately 40 percent of the variation in a multicenter clinical trial evaluating the effectiveness of tirilizad mesylate (77, 91). Intercenter variation was noted with a variety of intensive care treatments, including narcotic use for sedation, and with a number of physiological variables, including mean arterial pressure and cerebral perfusion pressure for a multicenter clinical trial evaluating the efficacy of hypothermia (92). Interestingly, recent studies with an experimental TBI model suggests that choice of anesthesia or sedation, including Fentanyl and Isoflurane, can have marked effects on outcome and in the context of hypothermia treatment (93, 94). This example demonstrates the potential impact that variation in standard care may play in recovery and outcome. Centers who can enroll small numbers of patients may contribute the most variability to standard care treatment regimens because they are often less likely to follow consensus recommendations for standard treatment (91). Misclassification of outcomes can also influence study results. Interestingly, one study reports, that as the numbers of outcome categories increase, the greater the likelihood of outcome misclassification and erroneous results (95). While dichotomous outcomes are not reasonable for each and every clinical trial, care must be taken to create effective algorithms for accurate data collection, and the use of pilot data may be helpful in determining an effective outcome measure with a minimum necessary requirement of categories. Subset analysis of data, even in negative multicenter trials, is recommended to identify potential subpopulations who might benefit from a particular treatment (96).

Recently, the NINDS May 2000 Clinical Trials in Head Injury Study Group identified and discussed many

of the issues associated with failure to produce positive results with several recent trials (91). The Study Group concluded that in order for clinical trials to be effective, it is essential to: (i) establish that a drug or proposed intervention is having the desired effect on a specific mechanism of injury *in vivo*, (ii) to obtain adequate pre-clinical data, (iii) target subpopulations of patients most likely to benefit from the treatment, (iv) standardize clinical care, (v) choose appropriate outcome measures or endpoints, and (vi) have reasonable expectations for treatment effect (91). Priority should be placed on conducting experimental and clinical studies aimed at understanding mechanisms of injury and recovery, since they are critical when designing future clinical trials and identifying possible therapeutic targets. Evaluating the most effective window of treatment, dose response curves, drug pharmacokinetics and drug delivery to the brain, and multiple models of experimental TBI are needed for adequate pre-clinical trial data (91). Utilizing injury related prognostic variables in the selection criteria for studies may allow investigators to effectively target subpopulations for particular interventions. Functional status at the time of entry into rehabilitation trials may be more prognostic of outcome and a relevant way to group patients than injury variables (91). Other intrinsic variables such as age, gender, and genetic make-up are emerging as important variables to consider in trial design (15, 97). Strict adherence to clinical care guidelines, centralization of some study variables (e.g. CT scan interpretation), collection of concurrent medications, and collection of only essential study variables may improve the management of clinical trials. Finally, smaller effect sizes (5–7.5 percent), the careful design and use of sensitive outcomes as well as the judicious use of relevant proxy variables may allow investigators to appreciate subtle treatment effects for specific interventions (91).

### **Alternatives to Clinical Trials and Research Design**

While randomized clinical trials are considered the gold standard for clinical research, they are not always feasible or practical for each research question. Ethical issues and the inability to obtain the resources necessary to conduct a full scale randomized clinical trials may preclude this study design (98). However, randomized clinical trials may have their own limitations in that they may not provide a representative measure of the effectiveness of the treatment in common clinical practice settings (99). Observational studies may be one alternative technique by which to study necessary research questions, particularly when treatment variables of interest are not assigned based on prognostic factors influencing outcome (98). Some reports suggest that effect sizes generated from well

done observational studies can be comparable to those obtained from randomized clinical trials (100). However, observational studies are vulnerable to confounding variables impacting the outcome variable of interest and require the use of covariate analysis. Common issues associated with exploratory analyses or observational studies, such as appropriate correction for multiple comparisons, avoiding type II experimental error, and appropriate sample size also need to be considered in the study design (101, 102), in order to provide accurate conclusions and a solid foundation for the design of a future clinical trial. Single subject research designs can be valuable, particularly in clinical practice, to determine effectiveness of treatments and lay the ground-work for larger studies (103).

### **Translational Research in TBI**

Translational research is an important area of focus for TBI in that it identifies mechanisms of injury and recovery and lays the groundwork for the conduct of clinical trials. Advances in genomics and proteomics may provide a novel approach to identifying and exploring therapeutic targets (104, 105). Utilizing functional imaging technology (106–109) or quantitative EEG (110) may be some contemporary avenues by which to explore injury and recovery mechanisms directly in the clinical population with TBI. However, the majority of translational research requires the effective use of experimental models that reproduce the physiological and behavioral sequelae associated with injury. Several models, including fluid percussion (111) and controlled cortical impact (CCI) (112) are commonly used in rodents. Characteristics of the CCI model include not only a representative contusion, but also reproducible brain edema and marked changes in cerebral blood flow in surrounding cortex (113). Rodent models are cost effective, can provide a relevant and reproducible injury, and are effective in studying a variety of behavioral paradigms (114–117). Rodents, however, are not gyrocephalic animals, and the use of larger animal models, including primate models, may be necessary to fully characterize pathology associated with diffuse axonal injury. Experimental models of TBI have largely been utilized to study acute pathology and neuroprotection, however, they can be a useful approach for examining long term outcome, mechanisms of recovery, and relevant rehabilitation interventions. For example, the CCI model recently was utilized to study the differential effects of gender and environmental enrichment, an experimental correlate to therapy, on behavioral recovery (118). In order for TBI rehabilitation research to move forward, collaborative efforts with other basic science disciplines, such as neuroscience and psychology, to tackle complex issues such as cortical reorganization, neural plasticity, and the effects of rehabilitation strategies like forced

use will be required (119). Future work will also require that researchers find ways to actively link studies involving acute mechanisms of injury and treatment inventions with central nervous system repair and recovery.

### Priority Areas for TBI Rehabilitation Research

In 1999, an NIH consensus group identified and published some research priorities in the area of TBI (120). Highlighted among these priorities include a need for epidemiological studies targeting different demographic groups and to study mild TBI. The therapeutic window for treatment interventions needs to be studied, and the neurobiology of clinical TBI, using state-of-the-art technology needs to be addressed. Specific prognostic equations should be developed, and the relationship between impairments and global outcome evaluated. Finally, the long term consequences of TBI and the developmental impact of TBI on children should also be a focus of study (120).

Several priority areas for TBI, injury prevention, and rehabilitation research have been set by primary federal organizations that fund TBI research. The National Institute for Disability and Rehabilitation Research's Long Range Plan has research priorities in the areas of employment outcomes, individual health and function, technology for access and function, and independent living and community integration (121). The development of sensitive and effective outcome measures is a priority. Research in rehabilitation science, disability studies, and disability policy are also current NIDRR research priorities. Investigators, particularly in the field of TBI rehabilitation research, have had a long history of utilizing NIDRR funding to evaluate important questions in the area of TBI outcome. The TBI model system centers (122, 123) have been an important part of this endeavor. NIDRR based collaborative networks for TBI research also foster increased interactions between a varied group of investigators and allow for the recruitment of large samples to answer important TBI rehabilitation research questions.

The Centers for Disease Control's (CDC) injury center interact with researchers in acute care and rehabilitation in order to "advance a broad based, multidisciplinary approach to injury" (1). Highlighted among their many priorities relevant to TBI are to (i) identify risk factors and develop and evaluate interventions for secondary conditions following TBI, particularly for patients not treated at state-of-the-art facilities; (ii) identify methods to ensure that people with TBI receive services; (iii) develop and apply methods for calculating population-based estimates of the incidence costs and consequences of those non-hospitalized after TBI; (iv) determine the impact of TBI on special populations; (v) develop and implement interventions for reducing disability after mild TBI; (vi) determine how the environment impacts disability after TBI;

and (vii) investigate the long-term effects of TBI on the health and longevity of persons with TBI. These priorities indicate that the CDC has a wide range of research opportunities for investigators to utilize that integrate aspects of secondary and tertiary injury control.

"Healthy People 2010" is a collection of national health objectives highlighted by the NIH as research priorities. The goals of Healthy People 2010 are designed to identify significant threats to national health and to establish goals aimed at reducing these threats. One priority of Healthy People 2010 is to eliminate health disparities among different segments of the population, including those with disabilities. In particular, Healthy People 2010 aims to "promote the health of people with disabilities, prevent secondary conditions, and eliminate disparities between people with and without disabilities in the U.S. population" (124). These particular aims suggest that National Institutes of Health (NIH) views disability related research, including research on assessing and preventing secondary conditions associated with TBI, as an important priority area of research.

In 2002, the NIH began developing its roadmap for medical research in the twenty-first century and identifying new pathways to discovery, research teams of the future, and re-engineering the clinical research enterprise (125). Future NIH funded TBI research will likely incorporate many of the new research paradigms outlined within this roadmap. TBI research teams of the future will likely be multidisciplinary in nature, integrating several distinct areas of science to evaluate broad research questions. NIH hopes to increase interactions between clinicians and basic scientist with the thought that this interaction will generate studies that are effectively able to translate basic research findings into meaningful changes in individual health. NIH is committed to training clinician researchers to take part in multidisciplinary and translational research endeavors. Contemporary and integrated networks of researchers able to conduct large-scale clinical trials to efficiently study relevant research questions and rapidly disseminate their findings in the context of best practices are a priority. Standardized data collection, sample sharing and the development of effective outcome measurements are also a priority. The NIH hopes to leverage significant advances in molecular biology, bioinformatics, computer science and engineering to encourage innovative ideas and perspectives that lead to seminal breakthroughs in scientific research that lead to improvements with human health. Finally, the NIH hopes to develop private-public partnerships to extend and accelerate research. As investigators incorporate this new vision into their scientific approach and programs of research, we will move forward in understanding key mechanisms of injury and recovery, and effectively identifying and implementing therapeutic strategies for the population with TBI.

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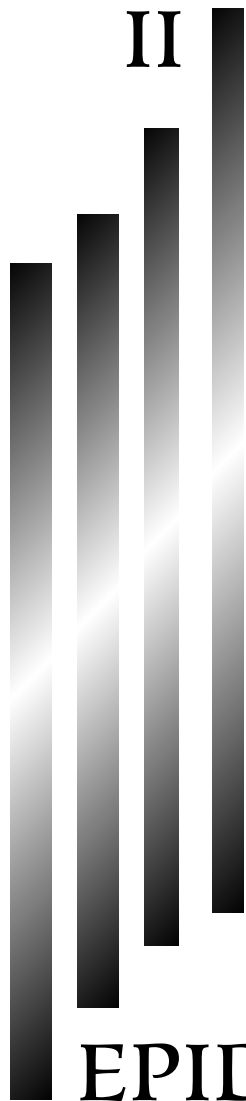
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**EPIDEMIOLOGY,  
PREVENTION,  
NEUROPATHOLOGY, AND  
NEURAL RECOVERY**

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# 6

## The Epidemiology of TBI: Implications for Public Health

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### INTRODUCTION

In the United States, traumatic brain injury (TBI) has been associated with more than 50,000 deaths annually, which is a third of all injury-related deaths. In addition, annually there are some 230,000 hospitalizations for nonfatal TBI, with an estimated 80,000 resulting in long-term disability (1). The incidence of TBI in the world population is unknown, but its magnitude is suggested by the *Global Burden of Disease Study* (2), which estimated the incidence of several categories of TBI severe enough to warrant medical care or result in death. For 1990, the estimates totaled over 9,500,000, but this may be conservative, as some categories (e.g., fall-related TBIs with short-term consequences) were not included. The uncertainty of these estimates notwithstanding, TBI clearly imposes a great burden on public health throughout the world. The purpose of this chapter is to characterize this burden by summarizing studies of the epidemiology of TBI, emphasizing findings about its frequency, risk factors, severity, and outcomes in populations. An understanding of the epidemiology of TBI is essential for developing effective prevention programs

and for planning appropriate health care services for those injured.

### DEFINITIONS

#### Traumatic Brain Injury

Case definitions for TBI have varied among epidemiologic studies, creating some difficulties in comparing their findings (3). For example, not all of the studies have included cases with skull fracture that lacked other documentation of neurologic symptoms or brain injury per se. In addition, the term “head injury” has often been used in place of TBI. An effort to standardize the epidemiologic case definition of TBI (as well as methods of data collection) led to the publication of *Guidelines for Surveillance of Central Nervous System Injury* by the Centers for Disease Control and Prevention (CDC) in 1995 (4). The CDC defined TBI as craniocerebral trauma, specifically, an occurrence of injury to the head (arising from blunt or penetrating trauma or from acceleration/deceleration forces) that is associated with any of these symptoms attributable to the injury: decreased level

of consciousness, amnesia, other neurologic or neuropsychological abnormalities, skull fracture, diagnosed intracranial lesions, or death.\*

The guidelines also provided a standard case definition for data systems, which includes International Classification of Diseases, Ninth Revision (ICD-9) (5), or International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (6), diagnostic codes in the ranges 800.0–801.9, 803.0–804.9, and 850.0–854.1 for cases regardless of survival status, with the addition of codes 873.0–873.9, 905.0, and 907.0 for cases resulting in death. Since the publication of the guidelines, most surveillance of TBI in the United States has relied on these definitions (7,8).

### Severity

In epidemiologic reports, TBI severity refers to the amount of acute disruption of brain physiology or structure. Assessments of severity derive from clinical evaluations conducted early in the course of acute medical care; sometimes they also take into account the results of neuroimaging tests. Epidemiologic studies have used various classifications of TBI severity, such as the Glasgow Coma Scale (GCS) (9), the Abbreviated Injury Severity Scale (AIS) (10), and ICDMAP (11,12), an approximation of the AIS based on ICD-9-CM diagnostic codes. Severity is of interest to the extent that it helps to predict the course and eventual outcome of the injury, but should not be confused with outcome.

The ordinal categories of these severity scales are sometimes combined into the broader categories of mild (or minor), moderate, and severe TBI (13,14). Defining the boundaries of these categories has been difficult, especially defining the minimum criteria of a mild TBI. To address the latter issue, CDC recently convened an expert panel; the consensus-based definition they developed may be summarized as follows:

Mild TBI is an injury to the head (arising from blunt trauma or acceleration or deceleration forces) that results in one or more of the following: any period of confusion, disorientation, or impaired consciousness; any dysfunction of memory around the time of injury; loss of consciousness lasting less than 30 minutes; or the onset of

observed signs or symptoms of neurological or neuropsychological dysfunction (15).

The term “mild” can be misleading if interpreted to mean inconsequential injury or injury with only minimal and transient effects. Clinical data indicate that some mild injuries have significant sequelae; the frequency with which these occur among people experiencing mild TBI remains to be determined by epidemiologic studies.

### Outcome

TBI outcome refers to survival status after injury and to the extent of impairment and disability after there has been an opportunity for recovery. Because of methodologic difficulties, relatively few epidemiologic studies have addressed TBI outcomes. Some of these have used the Glasgow Outcome Scale (GOS), a five-point ordinal measure of global outcome (16).

### Incidence and Prevalence

The measurement of TBI incidence (rate of occurrence of new cases) and prevalence (proportion of a population with TBI-related disability) requires population-based studies focused either on the entire population of interest or a representative sample of that population. Such epidemiological studies differ from descriptive studies of hospital case series, which constitute most of the clinical literature on TBI. Clearly, the latter cannot be assumed to reflect the entire population of persons with brain injury. Thus, such case series cannot accurately describe incidence rates or distribution of risk factors, causes, or severity in the entire population.

### Public Health Surveillance

Surveillance is the ongoing, systematic collection and analysis of information to monitor health problems (17,18). Recent TBI surveillance has often focused on temporal trends in the incidence of these injuries (8,19).

## METHODOLOGICAL ISSUES

### Availability of Data

Several data sources in the United States provide quantitative data for population-based assessment of TBI (20). The most easily obtainable of these sources are designed for other administrative purposes, e.g., hospital billing, and thus they contain only limited information regarding the clinical manifestations and causes of TBI. The information they include can sometimes be enhanced by linkage with other data sources, e.g., data abstracted separately from medical records. The following data sources

\*The CDC case definition of TBI was developed as a tool for public health surveillance, not clinical practice. As such, it attempts to identify not only cases of craniocerebral trauma where transient or persistent sequelae are noted but also cases where sequelae are possible. For this reason, the definition includes skull fractures in which medical records lack indications of neurologic injury per se, and also includes mild injuries in which records document only minimal and transient neurologic symptoms. The definition does not assume that the outcomes in such cases are necessarily adverse or of significant neurologic effect.

are widely available and useful for epidemiologic studies or surveillance.

**Mortality** The National Center for Health Statistics (NCHS) collects death certificate data from vital statistics records from all U.S. states and territories. These Multiple Causes of Death Data (MCDD) include information on demographics as well as the nature and external causes of injury, coded according to the International Classification of Diseases. The recent tenth revision of this classification (ICD-10) (21), incorporated major changes by forming new cause-of-death titles and codes and a restructuring of the leading causes of death (22). The effect of these changes on the comparability of mortality data collected before and after the implementation of ICD-10 has not yet been evaluated.

Most countries that belong to the World Health Organization (WHO) maintain some form of national death records using the ICD coding system. In general, developed countries have more reliable reporting systems than less-developed countries. Thus, comparisons of TBI mortality between countries must be made with caution, taking into account variability in the completeness of reporting systems and coding criteria.

**Morbidity** Developed countries often have national or regional data sets that allow descriptions of TBI-related hospital admissions, accurate to the extent that coding practices and reporting are reliable in individual hospitals. International comparisons of TBI using hospital discharge data systems are possible when uniform case definitions are used. The WHO *Standards for Surveillance of Neurotrauma* (23) contains such case definitions; these are consistent with CDC case definitions. The WHO Department of Injuries and Violence Prevention Program has many collaborating nations that provide aggregate data for international comparisons.

In the United States, the availability of such morbidity data is limited because the health care system is not centralized. Even so, several U.S. data sources are available:

The National Health Interview Survey (NHIS), conducted by NCHS, is an annual interview of a sample of households that in some years includes supplemental questions on injury. These allow estimates of TBI incidence, stratified by the level of care received (e.g., physician visit, hospital emergency department visit, or hospital admission). Survey data are limited by the accuracy of the information recalled by respondents.

The National Hospital Discharge Survey (NHDS), also conducted by NCHS, is an annual survey of patient discharges from a sample of

nonfederal hospitals. NHDS provides information on primary diagnosis and up to six secondary diagnoses, length of stay, payer information, and demographics. This enables estimates of the incidence of TBIs that result in hospital admission.

Many states aggregate claims data for hospital care to create hospital discharge data (HDD) sets. These data are standardized and coded according to the Uniform Billing form (UB-92), promulgated in 1992 by the U.S. Health Care Financing Administration (now the Center for Medicare and Medicaid Services). As long as states require all hospitals within their jurisdiction to report these data, HDD sets can enable reliable estimates of the incidence of TBI-related hospital discharges, and thus, they have become increasingly popular as primary sources of information for surveillance. These administrative claims data provide only limited information, however. In some state surveillance programs, additional information on severity, circumstances of injury, and short-term outcome is obtained by abstracting medical records in a representative sample of TBI cases identified from HDD sets.

Some emergency department data are also available with which to estimate the incidence of TBI among persons not admitted to hospitals. Since 1992, the NCHS's National Hospital Ambulatory Medical Care Survey (NHAMCS) has included a national sample of visits to emergency and outpatient departments of noninstitutional general and short-stay hospitals (24). In addition, some states maintain aggregate statewide emergency department visit data sets that can also be used for estimates of TBI incidence.

The NCHS National Ambulatory Medical Care Survey (NAMCS), another annual survey, provides information on ambulatory medical care provided by offices of physicians who are not federally employed. Although this data source affords some opportunity to estimate the incidence of injuries treated in an outpatient setting, the accuracy of physician office coding for specific diagnoses such as TBI has not been evaluated.

In many states, data on outpatient visits are available from state employee and workers' compensation insurance programs. These data sources provide detailed information on outpatient encounters for subscribers and their families. These sources may have limited use for the surveillance of minor injuries.



### Quality of Data Sources

The quality of the data that come from vital and health care data systems is limited for several reasons. First, because such data sets are often collected for nonresearch purposes, such as reimbursement, they may omit some important clinical information, such as indicators of outcome. Second, these data are often collected on a large scale and recorded, coded, and transcribed by many persons with varying degrees of skill. Third, diagnostic coding may reflect a need to maximize reimbursement. Finally, many hospitals and health care systems may lack the means to validate the coding derived from the medical record and ensure high quality data.

The availability of medical care and medical technologies, the integration of health care systems, the quality of the public health infrastructure (including vital records and medical examiner or coroner systems), and the availability of information technologies can all affect the completeness of TBI diagnosis and reporting. Not surprisingly, these vary greatly among nations and regions, and thus, international comparisons of TBI have to be carefully interpreted with consideration given to bias in case-ascertainment and information.

Although mortality data systems are less prone to error from duplicate reports, morbidity data aggregated from HDD sets may be subject to overreporting due to hospital readmissions and inter-hospital transfers, unless data can be linked to identify these occurrences.

The incompleteness of data elements that are critical for understanding TBI occurrence is a major problem in hospital discharge and emergency department data systems. ICD-9-CM external-cause-of-injury coding (E-coding) is usually incomplete in hospital discharge data sets (25,26), rarely exceeding 90 percent unless augmented by medical record review. In addition, the 5th-digits of ICD-9-CM codes, which provide additional clinical detail, are often incomplete. These are particularly useful, if coded correctly, to assess severity. Other crucial data that are often missing include source of admission, secondary payers, secondary E-codes that describe place of occurrence, and information regarding impairments and disability noted at the time of hospital discharge.

Finally, there are substantial limitations in the quality of clinical information that health care providers record, upon which accurate ICD-9-CM coding (including 5th digit information) depends. Notably, Glasgow Coma Scale scores are not recorded in about 40 percent of hospital medical records of people with TBI (8). Sometimes this is due to inherent difficulties in applying the GCS; for example, it may be difficult to assign an accurate score in the presence of injury complications or medical interventions such as periorbital swelling, intubation, or the use of drugs (e.g., sedatives or paralytic agents). Also, the GCS does not account for the amount of stimulation needed to obtain a response, which may affect its

reproducibility (27). In addition, the GCS is often not scored at consistent intervals following injury. Furthermore, numeric scales that are ordinal in nature, such as the GCS, are not linear. Thus, a 1-point change in a lower range of these scales may not represent the same degree of functional change as a 1-point change in a higher range (28). As well, the apparent simplicity of the GCS is misleading because it can be interpreted variously, even among neurosurgeons (29). Finally, its predictive value, especially when applied early, is limited (30).

## PUBLISHED POPULATION-BASED STUDIES

### Trends in TBI Incidence—United States

The incidence rates reported in selected epidemiological studies of TBI-related hospitalizations or TBI-related hospitalizations and death in U.S. localities are summarized in Table 6-1 (7, 8, 31–45). The rates should be compared with caution, because criteria for including cases and the use of rate adjustments vary (3). Still, these studies suggest that rates of TBI related hospitalization have decreased substantially in the last two decades.

From 1979 through 1992, the TBI-associated death rate in the United States decreased 22 percent, from 24.6 per 100,000 population to 19.3 per 100,000 (46). Most of the decrease resulted from a 42 percent decline in motor vehicle-related deaths, from 11.4 per 100,000 in 1979 to 6.6 per 100,000 in 1992. During the same period, firearm-related TBI deaths increased 9 percent, from 7.7 to 8.5 per 100,000, thus surpassing transportation crashes as the leading cause of TBI mortality. Rates of TBI-associated death due to falls and other causes decreased slightly during this period.

In contrast, an analysis of data from the NHDS for 1980 through 1995 documented a steep decline of 51 percent in TBI-related hospital discharge rates; they decreased from 199 to 98 per 100,000 per year over this period (47). The decline in rates of discharge occurred mainly among injuries classified as non-life-threatening. A comparison of findings in the 1979–1992 and the 1980–1995 analyses indicates a disproportionately large reduction in rates of nonfatal TBI resulting in hospitalization. This decrease may reflect some success in injury prevention, but it appears also to be the result of recent changes in admission policies that discourage inpatient care for less severe injuries (47). The apparent shift away from inpatient care underscores the need for surveillance of TBI patients treated in emergency departments and other outpatient settings.

### TBI-Related Hospitalizations and Deaths—Other Countries

The incidence rates reported in selected epidemiological studies of TBI-related hospitalizations or TBI-related hospitalizations and death are shown for other developed

**TABLE 6-1**  
*Selected U.S. Studies of TBI Incidence*

YEAR COMPLETED	LOCATION	RATE / 100,000	CASES INCLUDED*			INVESTIGATORS
			A	B	C	
1974	Olmsted Co., Minnesota	193	X	X	X	Annegers et al. (31)
1974	United States	200	X	X		Kalsbeek et al. (32)
1978	San Diego Co., California	294	X	X	X	Klauber et al. (33)
1978	North Central Virginia	175	X	X		Jagger et al. (34)
1980	Inner-city Chicago, Illinois	403	X	X	X	Whitman et al. (35)
1980	Rhode Island	152	X	X		Fife et al. (36)
1981	United States	136	X	X		Fife (37)
1981	Bronx, New York	249	X	X	X	Cooper et al. (38)
1981	San Diego Co., California	180	X	X	X	Kraus et al. (39)
1986	Maryland	132	X	X	X	MacKenzie et al. (40)
1992	Utah	108	X	X	X	Thurman et al. (41)
1992	Colorado	101	X	X	X	Gabella et al. (42)
1993	Colorado, Missouri, Oklahoma, and Utah	102	X	X	X	Centers for Disease Control and Prevention (43)
1993	Alaska	130	X	X		Warren et al. (44)
1993	Iowa	93	X	X	X	Schootman et al. (45)
1994	Seven states†	92	X	X	X	Thurman et al. (7)
1997	Fourteen states‡	70	X			Langlois et al. (8)

\* TBI cases reported include: A, live hospital discharges; B, hospital inpatient fatalities; C, non-hospitalized fatalities (determined from vital records).

† Arizona, Colorado, Minnesota, Missouri, New York (excluding New York City), Oklahoma, and South Carolina.

‡ Alaska, Arizona, California, Colorado, Louisiana, Maryland, Minnesota, Missouri, Nebraska, New York, Oklahoma, Rhode Island, South Carolina, and Utah.

**TABLE 6-2**  
*Selected International Studies of TBI Incidence in Developed Countries*

YEAR FINISHED	LOCATION	INCIDENCE RATE*	INVESTIGATORS
1974	Scotland	313	Jennet and MacMillan (48)
1974	Akershus County, Norway	236	Nestvold et al. (49)
1980	Trøndelag, Norway	200	Edna and Cappelen (50)
1986	Aquitaine, France	281	Tiret et al. (51)
1987	South Australia, Australia	322	Hillier et al. (52)
1988	New South Wales, Australia	100	Tate et al. (53)
1988	Cantabria, Spain	91	Vazquez-Barquero et al. (54)
1993	Finland	97	Alaranta et al. (55)
1993	Denmark	157	Engberg and Teasdale (56)

\* TBI-related hospitalizations or both hospitalizations and deaths per 100,000 population per year.

countries (48–56) in Table 6-2 and developing countries (57–61) in Table 6-3. Variations in case definitions, criteria for hospital admission, access to hospital care, and quality of national or regional health data sources, as well as different methods of identifying cases and collecting data hinder comparisons between these studies. These problems are especially difficult in developing countries (62). At present, there are too few published studies to form confident

conclusions about TBI incidence worldwide or to describe international trends. Population-based studies from South Africa, India, and Taiwan suggest higher rates in developing countries, however, with a predominance of road traffic injuries, but clearly more data are needed. The dissemination and adoption of international standards for TBI surveillance such as those published by WHO (23) should improve the amount and quality of international data.

**TABLE 6-3**  
*Selected International Studies of TBI Incidence in Developing Countries*

YEAR FINISHED	LOCATION	INCIDENCE RATE	INVESTIGATORS
1983	Six cities, China	55*	
1985	Rural areas, China	64*	Zhao and Wang (57)
1986–1987	Johannesburg, South Africa	316†	Brown and Nell (58) Nell and Brown (59)
1991–1992	Bangalore, India	122†	Gururaj (60)
1988–1994	Taipei, Taiwan	220†	Chiu et al. (61)

\* TBIs reported by household survey, number per 100,000 population per year.  
† TBI-related hospitalizations or both hospitalizations and deaths per 100,000 population per year.

### Recent Epidemiological Findings from the United States

**Mortality** A recent report from the CDC summarizes information on TBI deaths, using data from NCHS MCDD collected from 1989 through 1998 (19). During that decade, an annual average of 53,288 deaths were associated with TBI, a rate of 20.6 per 100,000 population. During this interval, TBI-related death rates declined 11.4 percent, from 21.9 to 19.4 per 100,000. Most of these deaths were related to firearms, transportation (involving motor vehicle occupants, pedestrians, bicyclists, motorcyclists, and others), or falls.

According to this CDC study, death rates among males were 3.4 times as high as among females (33.0 per 100,000 males and 9.8 per 100,000 females). Rates were highest among persons aged 75 years and older, with a smaller peak among those aged 15–24 years. The leading causes of TBI-associated death varied with age, with firearm-related injuries ranking first among persons aged 20–74 years, transportation-related injuries first among those under 20, and falls the leading cause among persons 75 and older. Rates for males were consistently higher than those for females: for firearm-related rates they were 6 times as high (14.5 versus 2.4 per 100,000); motor vehicle-related rates, over 2.3 times as high (9.9 versus 4.3 per 100,000); and fall-related rates, 2.5 times as high (3.2 versus 1.2 per 100,000). TBI-associated death rates for the 1989–1998 period differed by race as well: per 100,000 they were 27.2 for American Indians and Alaska Natives, 25.0 for African Americans; 20.1 for whites; and 11.9 for all other racial groups combined.

**Morbidity and Mortality** In the last decade, CDC has supported statewide surveillance of TBI-related hospitalizations and deaths in several states, using standard case definitions and methods noted above. An epidemiologic analysis of TBIs occurring in 1994 in Arizona, Colorado, Minnesota, Missouri, Oklahoma, New York (excluding New York City), and South Carolina (7) revealed an

annual incidence rate of TBI for the combined population of 91.8 per 100,000 (age adjusted to the 1990 U.S. population). This rate included TBI-related deaths (20.7 per 100,000), leaving an age-adjusted rate of 71.1 per 100,000 TBI-related live hospital discharges. For hospitalizations and fatalities combined, the median age at the time of injury was 32 years. The incidence rate was highest among persons 75 years and older (191.1 per 100,000) and among persons aged 15–24 years (145.1 per 100,000) (Figure 6-1). Two-thirds of TBIs (66.7 percent) occurred among males, with the crude rate among males about twice that among females (124.1 versus 59.1 per 100,000).

Transportation-related crashes (involving motor vehicles, bicycles, pedestrians, and recreational vehicles) accounted for 49 percent of all TBIs in the seven states; falls accounted for an additional 26 percent (Figure 6-2). Firearm use accounted for another 10 percent, and assaults not involving firearms accounted for 8 percent. Nearly two-thirds of firearm-related TBIs (66.5 percent) were classified as suicidal in intent. The leading causes of TBI varied by age in the seven states (Figure 6-3); falls were by far the leading cause among persons aged 75 years and older (126.6 per 100,000), while transportation-related crashes led the list for persons aged 15–24 (97.9 per 100,000).

A more recent report describes similar findings for nonfatal brain injuries admitted to hospitals in 14 states during 1997 (8).\* The age-adjusted TBI-related live hospital discharge rate for this 14-state population was 69.7 per 100,000, with age and sex distributions similar to those described in the earlier report from seven states. The more recent report describes differences in age-adjusted rates of TBI by race, with somewhat higher rates among American Indians/Alaska Natives (76.7 per 100,000) and African Americans (74.2 per 100,000) than among whites (63.0 per 100,000).

\*Alaska, Arizona, California, Colorado, Louisiana, Maryland, Minnesota, Missouri, Nebraska, New York, Oklahoma, Rhode Island, South Carolina, and Utah.

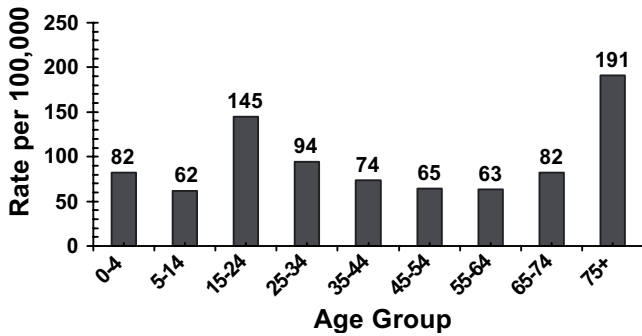


FIGURE 6-1

Rates of TBI-related hospitalization and death by age group\*—seven states,† 1994

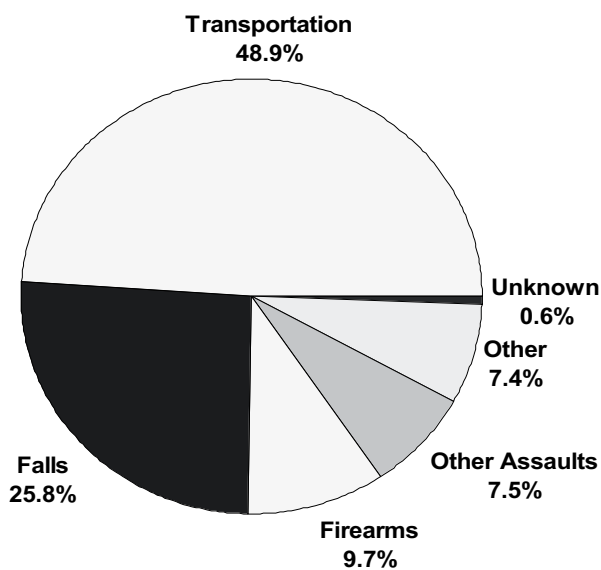


FIGURE 6-2

Proportions of TBI-related hospitalizations and deaths by external cause—seven states,† 1994

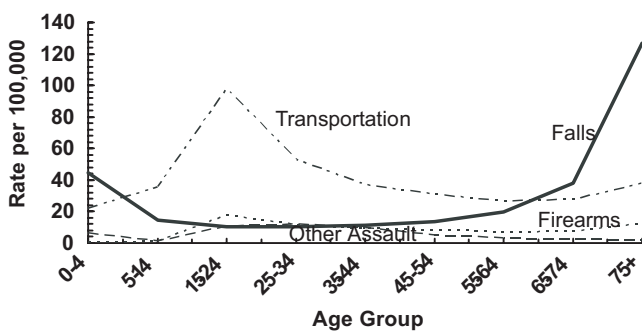


FIGURE 6-3

Rates of TBI-related hospitalization and death by age group and external cause of injury\*—seven states,† 1994

\* Rates not adjusted by sex.

† AZ, CO, MN, MO, NY (excluding NYC), OK, and SC.

**Nonfatal TBIs Not Admitted to Hospitals** In the United States, the NCHS's NHIS has provided some information on TBI treated on an outpatient basis (63). In 1991, an estimated 1.54 million noninstitutionalized U.S. civilians sustained a brain injury that resulted in loss of consciousness but was not severe enough to cause death or long-term institutionalization, according to self-reported NHIS data collected with the 1991 Injury Supplement. Of these 1.54 million persons, 25 percent received no medical care for their TBI; 49 percent, care in an emergency department or other outpatient site, and 9 percent, overnight hospital care; 16 percent were admitted to a hospital for 2 or more days. The limitations of the survey methods and respondent recall may limit the accuracy of these estimates. Data from the NHAMCS of 1995–1996 may provide a more accurate estimate of the incidence of nonfatal TBIs in which the patient was treated and released from hospital emergency departments (64). This analysis indicates an average annual incidence rate of 392 such emergency department visits per 100,000 population, or about 1 million visits annually.

**Severity and Outcome** Several measures of TBI severity have been used in epidemiological studies. The case fatality rate, which is the proportion of cases resulting in death, is the simplest epidemiological measure of severity as well as outcome. In the study of TBI-related hospitalizations and deaths in seven states during 1994, (7) 22.6 percent of all reported TBIs were fatal within the acute period of injury. Of all persons with reported TBIs, 16.9 percent died without being admitted to a hospital, while 5.6 percent died while receiving acute inpatient care. The case fatality rate varies greatly by cause; in this study, 90.4 percent of firearm-related TBIs resulted in death, but only 10.2 percent of fall-related TBIs proved fatal.

In the analysis of NHDS data for 1980–1995 described earlier, the authors used ICDMAP-generated ICD/AIS scores to estimate the severity distributions of hospitalized cases (47). In the NHDS data for the last 2 years of the study period (1994–1995), 52 percent were *mild* (ICD/AIS score 2), 21 percent were *moderate* (ICD/AIS score 3), 19 percent were *severe* (ICD/AIS score 4–6), and 7 percent were unknown. The proportion of TBIs classified as mild among the 1994–95 cases was considerably smaller than the corresponding proportion of 1980–1981 cases and was also smaller than proportions reported in earlier studies (3). These findings support a conclusion that persons in the United States with less severe TBI are now less likely to be admitted to the hospital.

**Incidence of TBI-Related Disability** Few studies have addressed the incidence of TBI-related disability. From limited available epidemiological data, Kraus estimated that in 1990 about 83,000 or more U.S. residents were

disabled by TBI. (3) The CDC published a similar estimate based on 1994 data from the NHDS and 1996–1997 data from the Colorado TBI Registry and Follow-up System (1, 65). The latter system surveyed TBI survivors one year after injury and measured long-term disability with the Functional Independence Measure (66). NHDS data indicate that during 1994, 230,000 persons hospitalized with TBI survived, and data from the Colorado TBI Registry and Follow-up System indicate that approximately 35 percent of hospitalized survivors of TBI are disabled 1 year after injury (7). Combining these figures suggests that more than 80,000 persons in the United States experience the onset of long-term disability each year following hospitalization for TBI. This estimate may be conservative, however, because it excludes the unknown number persons who are not hospitalized after TBI but still experience long-term disability as a consequence of their injury.

*Prevalence of TBI-Related Disability* Despite the recent publication of reports on the incidence of TBI-related hospitalization in several countries, few reports are available on the population-based prevalence of TBI-related disability and relatively little of the published data was collected with sufficient rigor to enable confident estimates. Most studies of disability occurrence after TBI have examined series of patients admitted to research hospitals. Such studies, by not including persons hospitalized in nonresearch and community hospitals, may not be representative of the underlying population. In addition, they do not address the outcomes of TBIs that are treated only in hospital emergency departments. These limitations notwithstanding, several of such studies—reviewed in other chapters of this book—have a sufficiently broad inclusion of participants to permit important generalizations regarding outcomes following TBI-related admission. Such studies document high proportions of patients who experience long-term sequelae, including substantial psychosocial and physical disabilities that are often associated with cognitive impairments (67).

The information obtained from population-based follow-up studies in Colorado and South Carolina is expected to enable more accurate estimates of disability associated with those TBIs severe enough to warrant hospitalization. In addition, the CDC has provided a provisional estimate of the prevalence of disability from TBI in the United States, based on preliminary follow-up data from the Colorado TBI Registry and Follow-up System and historical and current estimates of national TBI incidence. Together these sources suggest that approximately 2 percent of the U.S. population (5.3 million in 1996) are living with disability as a result of a TBI. (7) This estimate does not, however, account for disability among people with TBI who visited emergency departments or outpatient clinics but were not admitted. Improvements

on this estimate can be expected as more data are obtained and analyzed from these studies.

*Using Severity Indicators in TBI Surveillance to Predict Outcome* The Glasgow Coma Scale score is a widely used predictor of outcome, both mortality and disability (68–71), and yet its ability to predict the latter is limited in the population of TBI survivors who receive rehabilitation (72). Some research indicates that the prediction of the distribution of TBI disability outcomes in population-based studies may be improved by supplementing GCS data with information about computed tomography (CT) findings (73). Currently, state surveillance programs in the United States collect both GCS and CT scan data, but population distributions of severity based on the combination of these data elements have not yet been published. Other research has found predictive value in the duration of post-traumatic amnesia (74–78), and Nell and Yates proposed an enhancement of the GCS that incorporates a measure of duration of post-traumatic amnesia in persons with little or no depression of consciousness (79). Population-based studies that describe TBI severity with these measures have not yet been published; when available, such studies will help to predict the magnitude of ongoing health care needs among people with TBI.

*Economic Costs* Max and colleagues, who analyzed 1985 U.S. incidence and cost data for TBIs that resulted in hospital admission or death (80), estimated that total lifetime costs for those injured were approximately \$37.8 billion, with 12 percent for direct costs of medical care (hospital, extended, and other medical care and services); 55 percent, injury-related work loss and disability; and 34 percent, lost income resulting from premature death. A reexamination of this study that adjusted its estimates for inflation and more recent TBI incidence data, yielded total lifetime costs of \$56.3 billion for injuries sustained in 1995 (81). New studies are needed that use recent healthcare cost data to update this estimate.

Studies of trends in the economic cost of TBI are of particular interest in public health. The Model Systems Traumatic Brain Injury program, funded by the U.S. Department of Education's National Institute on Disability and Rehabilitation Research, collects data from multiple centers, enabling trend analyses of the cost of medical care for enrolled TBI patients. A recent study indicates that from 1990 to 1996, average daily inpatient charges in this group of patients increased by 98 percent for acute care and 41 percent for rehabilitation (82). During this interval, however, these increases were offset by reductions in average lengths of stay of 42 percent in acute care and 38 percent in rehabilitation. The authors note that the steady downward trends in length of stay for both acute care and rehabilitation raise concerns about diminishing availability of health care services to persons with

TBI. The generalizability of their findings is uncertain, however, because they came from a study population that was likely skewed toward more serious injuries. Still, these findings support the need for current population-based assessments of trends in costs and care for TBI.

### APPLYING FINDINGS TO PUBLIC HEALTH: PREVENTING TBI

The evidence reviewed in this chapter makes clear the great importance of TBI to public health. Despite progress in reducing the incidence of these injuries—especially those associated with motor vehicle crashes (19,46)—the need for more effective primary prevention programs remains. To be most effective, such programs must be guided by current findings regarding the principal causes of TBI—transportation injuries, falls, and violence—as well as an understanding of populations at increased risk and individual risk factors.

Because the primary prevention of TBI occurrence is incomplete, an effective public health response to TBI also requires concerted programs to minimize adverse outcomes and disability. Such secondary and tertiary prevention comprises acute care and rehabilitation of persons with TBI, the subjects of other chapters in this book. To this end we need comprehensive strategies to ensure that people with TBI have access to appropriate care and services and we need effective policies to promote their independence and integration into the community.

To help persons living with deficits from TBI, we need better information on the nature and scope of these disabilities, including who experiences disability, which rehabilitation treatment methods are most effective, and what services are useful and readily available. Population-based follow-up surveillance is needed to provide more precise information on the longer-term impacts of these injuries. Standard measures for TBI outcomes need to be refined so they will readily identify the types of impairment and disability most amenable to prevention through rehabilitation and social support. Better understanding of the relationship between the initial severity of an injury and its long-term outcome will help identify those persons who need ongoing medical care, rehabilitation, and other services. Such information will also help health practitioners and policy makers ensure that these services are available in the community.

### SUMMARY

This chapter has reviewed epidemiological measures and estimates of TBI incidence, severity, long-term outcomes, and cost. All of these findings indicate that these injuries have a major impact on public health. Effective primary

prevention programs are needed that are informed by accurate epidemiologic data regarding causes and the populations at highest risk. Doing this requires improved public health data systems that record those TBIs that do not result in hospital admission as well as those that do. More basic and clinical research is needed to improve the acute care and rehabilitation of TBI. Finally, more epidemiological research regarding TBI outcomes and disability is needed to develop policies that will ensure the availability of effective acute care, rehabilitation, and other services that will minimize disability among injured persons and promote their reintegration into the community.

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# 7

## Primary Prevention

*Elena Napolitano*  
*Jeffrey Radecki*  
*Elie P. Elovic*

### INTRODUCTION

The intent of this chapter is to review common prevention strategies and their overall effectiveness in this patient population, with an emphasis on the need for further preventative measures. The importance of these efforts will be obvious to readers after the following discussion that addresses the data on the incidence, severity, and consequences of traumatic brain injury (TBI).

Injury is the leading source of death for Americans under age 44 (1) and one-third of all injury-related deaths from 1979 to 1992 were associated with a TBI (2). Approximately 1.5 million Americans sustain a TBI every year (3). From 1979 to 1992, 50,000 American deaths and 230,000 hospitalizations occurred annually as a result of TBIs (2). In addition, each year over 80,000–90,000 people develop long-term disability secondary to TBI with approximately 14 million days of restricted activity secondary to TBI (4–6). The number of Americans who have some form of disability as a result of TBI is estimated to be around 5.3 million (7,8). The annual overall cost to the United States was estimated to be \$37.8 billion in 1985 and \$44 billion in 1988 (9).

In 1996, approximately 150,000 children and adolescents were left permanently disabled and in need of long-term follow-up as a result of unintentional injuries including brain and spinal cord injury (10). Injury mainly

affects the younger population and encompasses more years of potential life lost than any other cause with estimates yearly totaling 3.5 million years (1). Most individuals who have sustained a TBI are unable to return to work and if they do return, their work capacity is limited. The estimated morbidity cost (injury related work loss and disability) was approximately \$20.6 billion in 1985 (9).

There was a decrease in the incidence of TBI related death and hospitalization from 1979 to 1992. From 1974 to 1986, TBI incidence, morbidity, and death rate was approximately 50 percent higher than current estimates. Currently the TBI hospitalization incidence is about 100/100,000 (5). This differs from previous reports rates of 200/100,000 that were reported between 1974 and 1986 (7,11–13). The decrease may in part be a result of a decrease in severity of injury, overall change in admission policies, and a push to treat these injuries in the outpatient environment as well as possible benefit from prevention efforts. In 1980, the rate of TBI related mortality in the United States was 24.7/100,000; this had fallen 20 percent by 1994 to a rate of 19.8, with motor vehicle related mortality showing the greatest decline. With various prevention efforts such as use of air bags, seat belts, and child safety seats, mortality dropped 38 percent from 11.1 to 6.9/100,000 between 1980 and 1994.

## TRAUMATIC BRAIN INJURY VS. OTHER DISABLING CONDITIONS

TBI has often been called the silent, or invisible, epidemic (7), a stepchild that has only received minimal public awareness and dedication of financial resources to its treatment and prevention. This is a grave mistake, as the annual incidence of TBI is greater than that of the more widely known conditions of spinal cord injury, breast cancer, multiple sclerosis, and HIV (See Figure 7-1.). For example, there are 50,000 deaths per year as a result of a traumatic brain injury versus 16,273 deaths reported in 1999 as a result of HIV (14). The mortality rate for HIV has dropped over the past few years, which can be mainly attributed to public awareness, dedication to preventative measures, research, and treatment. The same trend is potentially possible in TBI if efforts are directed to awareness and prevention. It may take multiple strategies, targeting various communities, to enhance public awareness (15). Meeting communities' individual needs can possibly lead to implementation of more effective preventative measures.

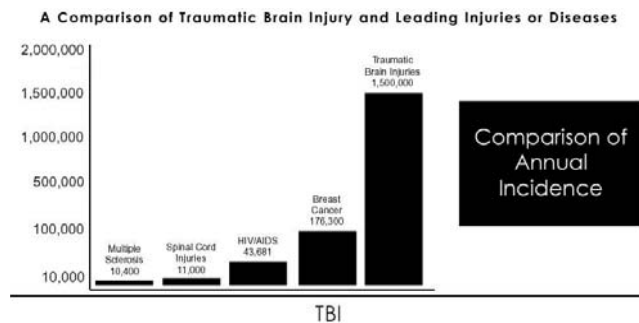


FIGURE 7-1

## ECONOMICS OF TBI: COSTS, BURDEN, AND ITS PREVENTION

There are monumental economic costs associated with TBI, when one includes both direct medical care and indirect costs such as loss of productivity. It was estimated that in 1985 the lifetime cost of injury amounted to \$38 billion for those injured enough to result in death or hospitalization (9). Ten years later, approximately \$260 billion dollars was spent on injury in the United States (16).

With the growing medical costs in today's world, the cost/benefit ratio of a prevention program is an issue of importance. Some of the more accepted preventative measures such as Hepatitis B vaccinations in newborns, child safety belts, bicycle helmets, and smoke detectors have proven to be very cost effective. Injury prevention programs vary in their cost effectiveness; however, many of them have shown their worth. In regards to TBI, programs such as zero alcohol tolerance for drivers under 21 years of age and graduated licensing have also proven to be of benefit (1).

A study that examined the time and money spent counseling families of young children regarding injury prevention efforts, reported that \$13 was saved for every dollar spent on counseling (17). Emphasis must be placed on community education for better public awareness. There appears to be a correlation between public awareness and the listener's educational level and income. This is an important point in patient education that should not be overlooked and should be factored into injury prevention programs.

There is a significant need to increase funding for prevention efforts. This may be problematic as funding may actually decrease as a result of an increased pressure to reduce spending by the federal government. As a result, it is probable that funding from the Preventative Health Services Block Grant will be reduced, which is a major funding source for injury prevention programs and chronic disease prevention (10).

## WHAT IS PREVENTION?

Prevention can be subdivided into primary, secondary, and tertiary prevention. Primary prevention efforts are designed to prevent the actual injury. Examples of primary prevention include screening tests, fall-proofing homes, traffic laws and their enforcement, salting of ice-covered roads, and education on topics such as drinking and driving. Primary preventative measures has been shown to work with other conditions. Adjusting workstations for individual workers have had an impact on decreasing musculoskeletal disorders and injury from their use (18). Secondary prevention is described as lessening the impact of the damage resulting from injury. Examples include engineering methods, such as automobile seatbelts and airbags, which have had a significant effect at controlling injury (18). Developments of advanced trauma care and emergency management services are examples of tertiary prevention, with their purpose being to lessen the secondary sequelae of injury (1).

The USPS Task Force was a large four-year multi-disciplinary effort to assess various preventative health measures. The summarized assessment contained 169 interventions in three different areas: screening, counseling and immunization/chemoprophylaxis. The predominant finding was that personal health behavior, such as smoking, diet and exercise, is the main contributor to mortality and disability. The task force emphasized the importance of physicians educating their patients while simultaneously giving them more responsibility for their own health. It was recommended that various strategies should be used to counsel the patients including support groups, written material and audiovisual aids (19).

## INJURY CONTROL THEORY

Originally, the general belief was that TBI was a result of accidents, which implied that all persons had equal

probability of sustaining injury (20,21). After a review of TBI epidemiology literature it appears that this may not be the case. Careful consideration must be made to a person's age, sex, and other individual risk factors that increase the likelihood of sustaining an injury (19). For example, falls among the elderly may be secondary to sedatives, antidepressants, lower extremity disability or balance impairments (5). There has been substantial work devoted to the identification of people at risk and developing effective preventive countermeasures (21,22) and as a result there has been a substantial increase in the science of injury control theory over the last 50 years

### THE HADDON MATRIX

The Haddon Matrix is a model that divides injury into various components including a host, vector and the environment, both physical and social, that the host and vector interact within. An elderly person falling on the ice and breaking their hip can serve as an example. In this case, the host is the injured human, the vector the age of the person and the environment is the weather conditions during the time of injury.

Haddon also identifies three different phases of injury, the pre-injury, injury and post-injury phases. This is comparable to the primary, secondary and tertiary prevention efforts mentioned above (1). Using these sets of variables a table can be created where each cell represents an area and a temporal component. All the different variables that contribute to an injury can be placed into one of the table's cells.

To best illustrate this concept, consider the factors related to a motor vehicle accident in the preinjury phase. Age and alcohol use would be placed in the host pre-crash or pre-injury cell, the vector would include the condition of the vehicle and the environmental cell would contain the roadway design. The cell, which includes the socio-economic environment, takes into account the affordability to the consumer and their safety risks. It would account for risks associated with purchasing an older cheaper vehicle without safety features or poorer road handling capabilities.

By studying the epidemiology of injury, efforts can be made at breaking various injury patterns in the different phases. Potentially the most efficacious way to prevent an injury is to target the vector or injuring agent and thereby alter the mechanism of energy transmission. Creating better designed cars, better engineered roads and improving conditions of the vehicle would greatly impact injury prevention.

### APPROACH TO HEALTH MAINTENANCE

To address the important issue of health maintenance there must be a comprehensive approach at controlling

injury and promoting health. It must include passive and active strategies, education and legislation. Passive strategies include those in which the host does not have an active role in its use (23). By nature, they offer protection to a larger percentage of the population and have the advantage of demonstrating effect without requiring any effort by the host that requires protection (24). Some examples of these include airbags, road barriers, fingerprint based gunlocks and car safety engineering. Active strategies are ones that require the host's participation, with the donning of a seat belt, avoiding driving when under the influence, motorcycle helmet usage and car seats as examples. Active prevention is dependent upon the public's awareness of such measures and their overall compliance with them. It may take a tremendous amount of societal effort to encourage the host to adopt these active measures of prevention. While this is a disadvantage as compared to passive measures, their potential for increased efficacy makes them potentially both important and possibly extremely effective when used in combination with passive measures.

In regards to education, professional health organizations are groups comprised of individuals who have met a standard of training and whose purpose is to serve the public. It is only natural that these groups use their position and expertise to further educational efforts to educate the lay community. This can be implemented through journals, publications and testimonies to legislative groups. The American Cancer Society, founded in 1913, is an example of a nonprofit voluntary health agency, organized to spread knowledge about cancer and is supported by voluntary donation (25). The Center for Disease Control is a federal agency responsible for surveillance of communicable diseases in the United States, investigation of epidemic diseases and promotes immunization and health education programs (18). On a smaller scale, education at the community and individual level by both physicians and other health care professionals must be emphasized as it can have a tremendous impact on injury prevention (15).

In general, changing human behavior can be a very challenging endeavor and there is still some controversy on the appropriate approach. Haddon stated that targeting the vector with passive interventions and the environment may be the most effective in decreasing death and injury. This does not negate the potential benefit of using a combined approach, of active and passive measures of intervention. An example of this is the use of seatbelts in combination with airbags. Each prevention method has shown its benefit, however using both together has been shown to be more effective than either one by themselves.

If one factors in legislation, to increase compliance with active prevention efforts further benefits can be attained. The states that strengthened existing seatbelt laws and adopted primary enforcement seatbelt legislation had

an estimated 79 percent compliance with belt use in 1998. This was an increase from 62 percent seat belt compliance in 1992 prior to the addition of primary enforcement legislation (1,26).

### DEVELOPMENT OF A COMPREHENSIVE INJURY PREVENTION PROGRAM

The components critical to development of a comprehensive injury prevention program are active and passive strategies, education and legislation. Engineering solutions are an important component of the passive interventions and include items such as energy absorbing car bodies, road barriers and air bags. Active strategies, such as education, are also critical, both at the individual and community level (1). Some of the most effective interventions include hands on demonstrations and reinforcement at subsequent visits (27). However, the listener is more inclined to change their behavior if there is some incentive to do so.

It has been shown that if only education is used then the general public may not change their overall behavior (28). Community based intervention programs combining education with legislative options has been shown to be effective in increasing bicycle helmet usage (15). Work performed in three separate Maryland counties explored bike helmet usage by children under three separate conditions. In one county, helmet use improved significantly when education and legislation were combined (43 percent increase). Another county, which used education alone, showed only an 11 percent increase, which was not statistically significant (29). The third county, which did nothing, actually demonstrated a decreased rate of helmet use from 19 to 4 percent.

Enforcement of legislation is critical to maximize its potential benefit, with seatbelts being an example. By 1984 passenger cars were required to have seatbelts, but only 15 percent of people used them while driving. By 1987 education combined with seatbelt legislation increased this rate to 42 percent. This was further increased to 62 percent when secondary enforcement laws were enacted for nonuse. A secondary enforcement law is one that allows the giving of a citation when the driver has been pulled over for another traffic offense. This rate stayed the same through 1998 in the states that used secondary enforcement laws. When some states increased legislation and enforcement efforts with the enactment of primary enforcement legislation, which allowed ticketing when the only infraction was seatbelt nonuse, compliance increased to 79 percent (26).

In summary, a comprehensive approach to injury control including active and passive measures, education at both the community and individual level and appropriate legislation is the most efficacious way to facilitate

injury prevention. It is necessary to take a multifaceted approach, targeting as many components of the Haddon Matrix as possible to promote injury prevention.

### MOTOR VEHICLE

To begin the exploration of TBI prevention efforts, it is most fitting to approach this issue by examining the leading cause of TBI in the United States: motor vehicle accidents (7). Motor vehicle accidents are the most common cause of brain trauma in the United States and are responsible for approximately half of all brain injuries each year (30). The prevention strategies that have targeted motor vehicles have resulted in a decreased occurrence of transportation related brain trauma. There has been a 38 percent decrease in motor vehicle related deaths from 1980 to 1994 (7). In 1970, there were 4.6 highway fatalities per 100 million passenger miles traveled. This number dropped 50 percent to 2.3 fatalities per 100 million passenger miles by 1989 (31). The reason for this reduction in fatalities is multifaceted and includes airbags, seatbelts, safety features and a higher legal drinking age, all of which will be further addressed in this discussion. Transportation related TBI prevention efforts could be approached, using both passive and active methods and, as with other preventative measures, the more comprehensive the approach, the better the overall effectiveness.

### AIRBAGS AND SEATBELTS

Airbags are designed to rapidly and automatically deploy during a frontal vehicle collision with the intent of creating an absorptive impact barrier between the vehicle's occupants and the automobile's front interior paneling. This barrier allows for the safer transfer of energy that occurs with impact. An airbag is deployed after the vehicle either comes into contact with a fixed obstacle, such as a brick wall, at 15 miles per hour or when it collides with an equally sized vehicle at 20 to 30 miles per hour. The entire cycle of deployment and subsequent deflation of airbags occurs within one second. It takes merely 1/20th of a second to inflate after impact with the deflation portion beginning within 4/20th of a second. The advantages of this rapid cycle lie in the ability of the driver to maintain control of the vehicle and also prevent trapping of passengers (32).

Advocacy for airbags has resulted in their installation as standard equipment in all passenger cars. Jagger has stated early in the 1990's that making airbags standard equipment would be of greater benefit in the prevention of TBI than any other prevention method (30). She surmised that of the number of patients admitted to a hospital who had acquired TBI, 25 percent could have been prevented

by the use of airbags. While they have been of some benefit, Jagger's prediction has been somewhat off the mark as will be discussed later in this section.

Airbags are designed to protect against frontal impact collisions and are not designed to prevent ejection from the vehicle, a major cause of vehicle collision mortality, which requires seatbelt usage to prevent. Another issue, is that they were designed to be effective with frontal injuries and are less beneficial with impact that do not occur between 11 and 1 O'clock with 12 O'clock as direct head on collision (32). Newly developed side impact bags are being introduced into the market that provide much needed protection against side and rear impact collisions and vehicle rollovers. The issue of side air bags is important because it is thought of as an important way of protecting the torso in a side impact collision. It is an alternative to padding as it occupies less space in the car. There are still challenges with perfecting this method of prevention such as the timing of deployment of the bag and length of time for inflation. The best location of deployment also needs to be determined to minimize the risk of injury, particularly those of the upper extremities (33). It is important to ensure that the bag does not deflate too rapidly and become stiff because as the volume of the bag decreases, it automatically gets stiffer (34). Women are particularly vulnerable as they tend to sit closer to the steering wheel. One must be careful in the design of an airbag system as excessive stiffness may result in head injury (35). It is also difficult to make a side bag that would be appropriate for all torso sizes. It was suggested by Parkin et al. that the ideal "smart" restraint system would be programmed for the sex and age of the patient. The literature is yet to determine if side airbags will prevent brain injury. They continue to hold promise as frontal airbags are not foolproof and have limitations in the area of the body that they protect and the type of collision it protects against. Further research in this area is both exciting and still warranted.

The combined utilization of seatbelts and airbags has been proven to be the most protective. In the National Highway Safety Administration's Third Report to Congress in 1996, airbags were reported to reduce fatalities in pure frontal crashes, excluding rollovers, by 34 percent and 18 percent in near frontal collisions. In this analysis, the fatality rate using airbags alone was reduced by 13 percent taking all crashes into consideration. This is in comparison to a 45 percent reduction rate using lap-shoulder belts alone and 50 percent reduction using both modalities (32).

The National Highway Traffic Safety Administration's Crashworthiness Data System reported interesting information regarding the efficacy of airbag and seatbelt use in moderate and severe injuries. Tests studying the effects of airbags alone did not demonstrate a statistically significant result as moderate and severe injuries were

reduced by merely 18 percent and 7 percent, respectively, when looking at all organ systems. This was in sharp contrast to the reported reduction of 49 percent and 59 percent with the use of a lap-shoulder belt system. Interestingly, the combination of both systems reduced risk by 60 percent. From this information one might conclude that airbags provide very little added benefit to the use of lap-shoulder belt system restraints. However, while injury severity to different body systems must be taken into consideration, TBI has been shown to be the major source of mortality in the multiple trauma occupant (36). With this in mind, a restraint system that protects against head and brain injury is of great importance. The use of manual lap-shoulder belt and airbags in combination resulted in an 83 percent and 75 percent reduction in moderate and severe head injuries, respectively. This data is significant when compared to the risk reduction of 59 percent and 38 percent with the use of a lap-shoulder belt alone. Although much of the risk reduction results from the use of the lap-shoulder belt alone, it is important to realize that lap-shoulder belts must be "used," which differs from the automatic deployment of an airbag restraint system.

The preventative benefits of seatbelts and airbags are clearly demonstrable. However, there have been a number of injuries associated with their use. Some of these injuries include spinal, brachial plexopathy, liver lacerations, small bowel tears, traumatic hernias, aortic tears, ocular and facial trauma, neck sprains, kidney trauma, sternal fractures, lung perforation, and placental/fetal injury (37-55). Airbags have also been reported to cause a number of injuries including skull fracture and facial injury (56-58), ocular trauma (59-63), burn injuries (64-66), reflex sympathetic dystrophy (67,68), extremity fracture (69, 70), chest injuries, spinal injury (71,72), ear and hearing loss (73,74). There is substantial evidence that children are most susceptible to injury due to airbag deployment (59,71,75-81). These injuries have been severe and even fatal in situations where children have been both properly and improperly positioned (59,71, 75, 80,82,83). Efforts are currently underway to ensure that the protective benefits of airbags are extended to include children.

## MOTORCYCLES

TBI due to motorcycle accidents is a serious problem in the United States. Although motorcycle accidents account for only 6 percent of all related transportation accidents, it may very well be the most dangerous form of transportation (84). There have been nearly 10,000 deaths related to motorcycle accidents from 1989 to 1991(85) with an additional 15,000 motorcycle deaths associated with head injury from 1979 to 1986 (21). A fatality rate of 1.2/100,000 and a hospitalization rate of 24.7/100,000

were reported in a study from Connecticut with 22 percent of injuries occurring to the head, brain, or spinal areas (86). Comparatively, a study reported from New Zealand found a higher mortality rate of 3.6/100,000 and hospitalization rate of 80.4/100,000 related to motorcycle accidents (87).

Factors related to motorcycle fatalities include driver error (76 percent), most commonly excessive speed (21), failing to wear a helmet, and elevated blood alcohol levels. Amongst all methods of transportation, alcohol seems to be the greatest problem for motorcycle drivers with a study finding that they have the highest rates of both alcohol use and legal intoxication (88).

Probably the most critical mitigating factor relating to TBI and fatalities due to motorcycle accidents is the utilization of helmets. A study in 1982 reported that a helmetless rider has a 2.3 times greater likelihood of having head, neck, or facial injury and are 3.19 times as likely to suffer a fatality than those who wear helmets (89). Bachulis et al. (90), found the rate of brain injury to be double and severe brain injury six times more likely in helmetless riders. Similar findings were reported by Gabella et al. (91), with brain injury occurring 2.5 times as often in riders without helmets. The benefits of helmet use laws have also been demonstrated. After the implementation of a mandatory helmet law in Spain a 25 percent reduction in fatalities due to motorcycles related accidents was observed (92), as well as a decrease in injury severity, shorter hospital lengths of stay and better outcomes. Similar legislation passed in Taiwan resulted in a 33 percent reduction in head injuries (93). Similar findings have been reported from other areas of the world after mandatory helmet laws were enacted. The overwhelming result of this legislation has led to a reduced rate of overall fatalities, TBI related fatalities, overall TBI incidence, injury severity (92–99), length of hospitalization (96,97), and overall cost to society (96,97,100).

Despite this strong evidence from countries around the world, there are still a number of states across the United States that have not enacted mandatory helmet laws. In 2001, there were three states with no helmet legislation, 27 states with helmets required solely for teenage riders and only 20 states with mandatory helmet use for all motorcycle riders (100). Many states have had mandatory helmet laws in the 1970s that have since been repealed or revised.

In 1967, the Federal Government required states to pass a motorcycle helmet law in order to continue to receive federal safety funds. As a result, by 1975, 47 states had passed legislation requiring the use of helmets. However, as opposition mounted against the use of helmets, Congress overturned the helmet requirement. Following this action, more than half of all states with mandatory helmet laws revised their laws (101), with a resultant

decrease use of helmets in those states. Within 9 months of the repeal, the states of Texas and Arkansas saw a decline in helmet usage from 97 percent to 66 percent and 52 percent, respectively. There was a concomitant increase in overall motorcycle injuries, head injuries, and an increased proportion of those injured having suffered head injuries according to data obtained from the Arkansas Trauma Registry (101). This trend was also seen in Miami Dade County with an increased incidence of TBI and fatalities in the post repeal era that saw helmet usage dropping from 83 percent to 56 percent (102). Bledsoe et al. (103), reported on the Arkansas experience of helmet law repeal. A 6-year retrospective review of the trauma registry compared the results of the three years prior to repeal as compared to the three years afterwards. There was no statistical change in total and fatal collisions; however there was a major increase in nonhelmeted deaths at the scene of the accident. The nonhelmeted had significantly higher Abbreviated Injury Scores involving the head and neck, more expensive, longer ICU stays and substantially higher nonreimbursed hospital charges. This of course was a cost borne by the remainder of the community.

As mentioned above, the financial costs to society following the repeals of mandatory helmet laws have been substantial. A study in Texas concluded the median cost of motorcycle related injury increased 300 percent to \$22,531 per event, with TBI costs increasing 75 percent to over \$32,000. Most of these costs exceed limits set by insurance coverage and, so, the financial burden often falls on society (104).

Another issue that also arises is the relationship between alcohol and motorcycle driving. Since handling a motorcycle requires more coordination and judgment than driving a car, there may be a need to lower the blood alcohol level that classifies a motorcyclist as being under the influence. This is supported by a study that examined the blood alcohol levels of drivers of motorcycles and cars brought to trauma centers, with the motorcyclists having lower levels (105). This may indicate that a lower level of acceptable blood alcohol levels may be needed to determine when a motorcyclist is considered to be under the influence.

## ROADWAY DESIGN

Accident prevention can also be achieved by identifying hazardous road locations with specific collision patterns. Various approaches can be used to correct these accident-prone areas through road engineering and technology. The first step in this area was in the 1930's when skidding resistance was added to wet roads (106). It was not until 20 years ago that a major movement in developing safer roads was initiated. *The Road Safety Code of Good*

*Practice* was a publication from the Local Authority Associations that included engineering in addition to education and enforcement, the three E's, for better road safety (107). One study attempted to identify crash problems on various urban arterial streets in Washington, DC (108). Data was retrieved from police reports of a total of 2013 crashes. The locations that had a large number of crashes were analyzed to identify pre-crash movements and travel directions of the crash – involved vehicles. It was found that, at some intersections, drivers had difficulty turning left from a private driveway whereas some intersections had extremely high traffic speeds with crashes likely to occur at the end of a ramp. Left turn signals were not provided at some of the intersections. Based on the analysis of the accident data recommendations were then provided. Changes made included the addition of left turn signals, prohibition of left turns from a driveway, improvement of storm drainage, increased pavement skid resistance as well as the initiation of pavement milling. It was also noted that stopped buses obstructed drivers' visual fields. Relocating bus stops, as well as removing large fixed objects, was a simple intervention that was effective in reducing accidents.

Sabey suggested that the use of four investigative techniques could be the foundation for intervention and treatment of the problem. These four areas included *single sites* where accidents cluster or "blackspots", *mass action* or locations that have common accident factors, *route action* or lengths of road with above average accident rates and *area action* including areas requiring a more global approach aimed at dealing with scattered accidents. He also provided examples of proposed treatments for each of the four variables. For instance, route action could be addressed with road marking to deter overtaking, increasing skidding resistance or installing roundabouts at key junctions to provide access to adjacent neighborhoods. In one trial of a 3km road with a large number of accidents per year, a roundabout was added as well as a new light to control crossings in addition to right turn bans. This resulted in a 12 percent reduction in accidents that resulted in injury (106).

Rear end collisions can also be reduced by engineering methods. In British Columbia, road factors account for about a third of collisions (109). The Insurance Corporation of British Columbia (ICBC) has provided funding for road improvement programs and countermeasures for rear end collisions since 1993, with the amount of funding from the ICBC having been increased substantially from 1993 to 1996. Some interventions that resulted from this movement included creating left or right turn lanes in areas where there are a large number of turning vehicles, acceleration/deceleration lanes, medians with turn protections, prohibiting turns and/or providing a special phase for left turning vehicles. These interventions resulted in a decrease of rear end collisions by 20–40 percent (109).

Simple techniques such as enhancing signal visibility also resulted in a decrease frequency of rear end collisions.

Speed bumps may be of value but this is controversial. Some argue that alone they may not reduce a driver's speed but may be effective if used in combination with other traffic control techniques (110). Further studies are still warranted. Other intervention methods such as matured in-service red light cameras (RLC) at T-intersections have also shown to result in an increased stopping frequency at these junctions. One study looked at three T-intersections in Singapore and found that the odds ratio to stop when approaching a camera was slightly higher than 17 times that if there were no camera surveillance (111).

The "three E's" education, engineering and enforcement are all important parts of injury prevention. Although there have been improvements noted in the roads over the past few years, there is still a need for further efforts, including assessment and treatment of accident-prone locations. There still is a strong need for further funding and legislation in this critical area of injury prevention in the United States.

## FALLS

Falls have consistently been identified as the second most common cause of TBI (11–13,112–115). They occur in the greatest number among young children under the age of 5 and in the elderly (21). Younger children have a much larger head-to-body ratio and thus the head strikes the ground more frequently during play (116). Also as a result, a fall of only a few feet can have serious consequences in young children (117). Over two decades ago, falls from extreme heights accounted for 12 percent of all unintentional traumatic deaths in New York City children. Overall, in the United States, it has been estimated that falls comprise almost 9 percent of pediatric trauma deaths (118). Benoit et al. demonstrated that falls accounted for 41 percent of admissions to a suburban hospital for children age 0 to 14 years of age (119). Turning our attention to the elderly, fatalities as a result of TBI are most common over age 75 and falls are the number one cause of TBI in the elderly (7). Jagger et al. found that there was a stable pattern of occurrence of fall related TBI up to about 59 years old. Between the ages of 60–69, there was a dramatic rise in the occurrence, which continued to rise in those 70 years old and older (13). The financial burden from falls is enormous. In 1994 the estimated cost in the United States from falls approached \$20.2 billion (120).

Efforts at fall prevention have been effective with legislation and education. In 1972, the New York City Department of Health developed a health education program termed "Children Can't Fly." This initiated installation of window guards in all New York City apartments



that had children less than 11 years old residing in them. This resulted in a 96 percent decrease in falls from windows after implementation (118). The use of safety devices for windows in suburban areas has also shown to be helpful (119). There have been positive results in fall prevention both abroad such as in Sweden (121), as well as in American urban neighborhoods (122,123).

The issue of playground related falls can be addressed by the use of protective surfaces including adding a safe 12 inch border of a soft material such as wood chips, and sand or rubber around the play area (123–125). Adult supervision and education of the parents is still critical. Educational efforts directed at both children and the communities have also been shown to have benefits (126,127).

Fall prevention in the elderly requires several strategies that often require a doctor's input. Physicians must identify various factors that may contribute to falls in the elderly population. Miller et al. (128), mentioned four common issues that have been implicated in increasing the risk of falls in the elderly. They are postural hypotension, gait and balance instability, polypharmacy and the use of sedating medications. Other host related factors that have been associated with falls include musculoskeletal or neurological abnormalities, visual disturbances, dementia (129) and frailty (130).

Balance deficits in the elderly appear to be related to the deterioration of various input systems necessary for postural control. It has been demonstrated that in subjects over 70 years of age, there is a 40 percent reduction in sensory cells of the vestibular system (131). These elderly adults are more likely to fall if other systems required for postural control, such as vision and proprioception, are impaired (132). Impaired balance in the elderly can also be attributed to multiple deficits in the neuromuscular system. It has been consistently shown that disuse atrophy; motor weakness, deconditioning, abnormal tone and posturing contribute to impaired balance in the elderly (133,134). There may be generalized slowing of central-processing areas in the elderly that involve integration and coordination of multiple inputs and outputs in the brain including the motor cortex, basal ganglia, and cerebellum (133). Lesions within these pathways, such as that sustained by an ischemic stroke or intracerebral hemorrhage, may compound the problem. It is also important to realize that approximately one third of patients with severe closed head injury experience subsequent postural imbalance due to disruption of these various pathways (135).

Assessing patients for balance dysfunction is an important component in prevention. Various measures at measuring body sway have been looked at for reliability and repeatability in assessing our elderly population. One method, such as the posturographic quiet standing test, has been referred to in the literature. Helbostad et al.

evaluated subjects after asking them to stand as still as possible for thirty seconds. Task conditions were performed in random order amongst the subjects and included both eyes open or closed, wide or narrow stance and firm or compliant surface. Some patients were also asked to perform a cognitive task. It appears across all domains one can consistently and appropriately assess the frail elderly with repeated testing. Clinicians need to develop simple assessment measures, such as those described, that can be taken into the office setting. In this manner clinicians can initiate preventative measures once frail elderly patients at risk for balance instability and falls are identified (136).

Prevention must then be aimed at the various contributing factors. Balance training in physical therapy can be directed at lower extremity strengthening as well as proprioceptive and visual system training with repetitive feedback and continual cueing. Various approaches have been tried to enhance balance in therapy. The utilization of force-plate biofeedback system to improve standing ability has been reported to have positive effects (137). There is no standard physical therapy program or protocol for balance training and more research in this area is warranted. In addition to targeting the physical aspects, one must address a common, iatrogenic and possibly avoidable cause of balance impairment in the aged population and that is identification of polypharmacy. It appears the prevalence of inappropriate medication use in the elderly appears to be 20 percent in both the US and various countries in Europe. The result may lead to balance instability, sedation and confusion in our elderly population. Physician awareness of those at increased risk, such as elders treated with psychotropic medications and those with depression is important as it allows us to target modifiable variables as well as to avoid inappropriate prescription writing. Physicians must constantly readdress prescription medication to avoid both inappropriate use and polypharmacy (138). It is important to review all medications and try to decrease or eliminate the medications that may not be absolutely necessary (139).

The environment plays an important part in falls of the elderly. Speechley, M & Tinetti, M (130). found in a sample community of elderly persons that 15 percent of fallers did not have a chronic intrinsic risk factor and would not be considered frail. It appeared that environmental risk factors played a major role in the robust elderly population of fallers. Thus the elderly population must be counseled on safe performance of certain physical activities, such as climbing stairs and ladders and avoiding hazardous obstacles around the house such as throw rugs. The national bureau of standards has identified various household factors contributing to falls in the elderly. It was estimated that highly waxed floors, loose rugs, sharp furniture, poor lighting or problems

with tubs and showers have contributed to 18–50 percent of falls (21). One study demonstrated that 10 hours of non-skilled time and \$93 of supplies per person was all that was needed to make an elderly person's environment substantially safer (140).

Physicians can play an important role in fall prevention, especially after a first fall. More aggressive efforts at assessing the cause of falls are needed by physicians. Risk factors for osteoporosis should be identified as low bone mineral density (BMD) has been shown to contribute to falls. BMD screening must be considered in high risk patients such as chronic steroid users, those with a sedentary lifestyle and patients on antiepileptic medications. In one study, approximately 75 percent of women have never been screened for bone loss and less than 1/3 ever received recommendations for BMD screening. Osteoporosis prevention strategies including calcium supplementation can then be initiated when appropriate. It has been shown that most people in the US have inadequate calcium intake, making education with each visit necessary in our clinics. Education on the reduction of alcohol and caffeine intake in addition to the encouragement of weight bearing exercises should also part of our management plan. It is also important to address hormone status in addition to frequency and dose duration of steroids in chronic steroid users (141).

## SPORTS AND RECREATIONAL INJURY

Recreational and sporting activities can be a significant cause of TBI with the majority of injuries being concussions (11,12,21,113). Unlike musculoskeletal training the brain cannot be conditioned to withstand the energy assault that is the cause of concussion (142). Therefore preventative efforts must instead be directed at improving equipment safety, behavior of the athlete, development of rules to mitigate risks and rigorous enforcement of rules and regulations to promote safety and prevent injury. This includes proper equipment design such as helmets for contact sports, sport rules that discourage dangerous activities and training and educational efforts for coaches and participants.

### CYCLING

Bicycle related TBI is a significant concern given their large numbers each year. Every year 1,300 people die from bicycle related accidents, almost half of them under 21 years of age (120,143). Financially, the cost of non-fatal bicycle injuries in children under 14 years of age approaches \$113 million every year (120). Fife et al. in a study conducted in Dade County Florida found that serious injuries related to bicycle riding were sustained

in 676 out of 1,252 total injuries. Almost half of the serious injuries were located in the head and neck region (144). In patients admitted to a hospital secondary to a head injury the risk of death was 20 times higher for those who were not wearing a helmet (145). Spence et al. (146), evaluated fatal bicycle accidents in children aged 0–15 years old in Ontario from 1985–1989. They found that 70 percent of the accidents were a result of the cyclists themselves. In a similar study, the cyclist was responsible for 78 percent of all bicycle accidents with the major errors reported as riding through a stop sign (22 percent) and emerging from a minor road without caution (27 percent) (147). It was pointed out by Spence et al. that children this young might not have the psychomotor skills to ride safely in traffic. Instead the goal should be to prevent these children from riding on busy streets.

The most effective way to immediately protect the cyclist is to have him wear a helmet. In five case controlled studies that were reviewed, the data demonstrated that wearing a bicycle helmet had a large impact on reducing the risk of head or brain injury during a crash or collision. Estimates regarding the effectiveness of helmet use is that they decrease the risk of brain injury by 88 percent, severe brain injury by at least 75 percent and facial injury, particularly in the upper and mid facial regions, by 65 percent (148).

Thompson et al. (149), performed an extensive review of the literature to evaluate risk reduction for cyclists and helmet use during riding. The authors found that helmets were beneficial in the reduction of head, brain and severe brain injury in all age groups and included not only bicycle injuries but also motor vehicle and other types of crashes. The reduction in risk was estimated to be approximately 70 percent. This is a conservative value when compared to the numbers suggested by Koplan et al. in their CDC sponsored work, which reported a risk difference of 85 percent for head injury and 88 percent for TBI (120).

Helmet usage is only one component of the Haddon Matrix in regards to cycling injuries. As stated previously, a comprehensive approach is the most effective intervention for injury control and this must be incorporated for bicycle injuries. Passive measures such as helmets, road engineering, bicycle lanes and speed bumps must be employed (120). Active strategies such as modifying cyclists behavior and counseling children on safety skills while riding must be aggressively pursued. Helmet use should be mandatory for all child cyclists and legislation is still warranted in all states given its overall effectiveness.

### BOXING

As expected the sport of boxing where the participants attempt to give each other concussions has the highest rate of TBI. Atha et al. (150), compared the blow thrown

by a top quality heavyweight to a 13-pound mallet swung at 20 miles an hour. In this sport record keeping in regards to brain injury has not been as precise as in football but between the period of 1945 and 1979 there was documentation of 335 deaths from boxing related head injury (151). In one report, the incidence of TBI in professional boxers was estimated to be approximately 20 percent (152). In 1983 it was reported that minor head injury rate for amateurs was 5 percent which increased to 6.3 percent at the professional level (153). Fatalities at both levels are substantial (154). Various risk factors that have been identified that increase the chances that a boxer will sustain brain injury include career length, number of bouts, poor showings in the ring and apolipoprotein (APOE) genotype.

There has been an increase in the public's awareness of boxing related brain injury with Muhammed Ali's illness over the years. Various preventative measures have been attempted such as guidelines for determining when a player should return to play after a head injury. For instance, The National Amateur Athletic Union (AAU) Junior Olympic Boxing Program specifies the length of time a participant must remain out of competition after a knockout. Wilberger and Maroon, noted that the New York State Boxing Commission enforced a mandatory suspension of 45 days for mild concussions and 60 and 90 days for moderate and severe concussions (151). A problem identified with professional boxing is that there is not enough consistency between the various states. A boxer who has been suspended in one state may be able to participate in another state without any restrictions. Other preventative measures such as changes to increase ring safety and improved monitoring by the referee and an on site physician have resulted in decreased mortality (154). There is a strong need for physicians to take a more active role in education of both the amateur and professional athletes as well as all others such as all referee's and ring side physicians. LeClerc and Herrera (155) have suggested that physicians must take an active role in educating the public regarding the risks of boxing. Their statement, "a watchful agnostic position among sport physicians is no longer justifiable" is a call to arms for health care providers to work diligently to educate the public concerning the dangers of boxing. While abolishing boxing may be an ultimate, but unrealistic goal, one must at a minimum strongly advocate for even greater safety measures (21).

## FOOTBALL

The game of football has been associated with an increased risk of sustaining a TBI. The National Football Head and Neck Injury Registry reported 59 intracranial football injuries that resulted in death between the

years of 1971 and 1975. In 1974, Blyth and Mueller (156) reported that while TBI accounted for only 5 percent of overall football injuries it accounted for 70 percent of the fatalities, with 75 percent of them occurring during tackling. The estimates for football related TBI are up to 250,000 concussions and 8 fatalities every year nationally. From 1985 to 1994, high school players sustained 81 percent of head injuries and 100 percent of cervical spine injuries (157). Furthermore, up to 20 percent of high school football players sustain a concussion per season played (1,158,159).

Given the popularity of the sport and interest to play among high school athletes, it is a sport that will likely continue to have many fans and participants. The focus must therefore be on injury prevention in addition to good clinical judgment in removing players from play at the greatest risk. The highest percentage of head and cervical spine fatalities associated with football was between 1965 and 1974. There was a significant decrease in head fatalities from 1985 through 1994 representing 5.4 percent of the fatalities from 1985 to 1994 (157). This is attributed to the multidisciplinary team involved in the football family including coaches, administrators, athletic trainers, physicians, national organizations; all of whom have provided education and public awareness.

Prevention efforts utilized for football have been effective. The issue of legislation and enforcement as well as passive and active strategies should again be revisited. With immediate punishment and consequences from illegal plays called by the officials, illegal dangerous plays can be discouraged and their incidence greatly reduced. There was a key rule change in 1976 that played a role in reducing head and spine fatalities. The rule prohibited initial contact with the helmet, also known as "head butting", or face mask, also known as "face tackling", when tackling or blocking. Tackling was responsible for 40.6 percent of all head fatalities from 1985-1994 and it is therefore imperative to adhere to this rule as a violation of it may result in a serious injury (157). There have been other important preventative efforts associated with football which include preseason conditioning, safe use of equipment and training for proper technique (160). In addition, proper fitting of helmets and physician evaluation post injury are also key components to any prevention program (21).

Second impact system is a potentially fatal complication that can result from repeated injuries prior to recovery from previous injury. It is important to mention this syndrome in the discussion of football related injuries. It may be missed clinically and appear as a minor injury but can be associated with massive cerebral edema, resultant brainstem compression and possible death (161). There are very few warning signs that would clue a physician to make the diagnosis of second impact syndrome. It is therefore important to abide by guidelines published

by the Colorado Medical Society regarding assessing concussive symptoms during play. These are considered the best guidelines for return the play post concussion (158).

## SOCCER

Another major sport that can account for a significant number of TBI is soccer or football to the rest of the non North American world. It has been estimated that head injuries account for between 4 and 22 percent of soccer injuries (162). Soccer is increasing in popularity and is considered to be the most popular sport worldwide. There were more than 40 million amateur participants noted in 1989 (163). Due to the large number of participants worldwide, the number of potential injuries can be significant, even if the rate of injury, may be lower than that of other higher contact sport (164). There is one Australian study the estimated injury rate occurred 96 per 1000 player hours (165). In Sweden, soccer is the number one source of recreational related injury with a rate of 39 percent reported (166). Data collected in Norway over an eight-year period, noted that 45 percent of all sports related head injuries were accounted for by soccer (167). Tysvaer and Storli looked at 69 active soccer players and 37 former players of a Norwegian national team and found that one third of the players had central cerebral atrophy and 81 percent had some form of neuropsychological impairment (162,168,169). Dvorak et al. have worked out both a risk analysis for prediction of injuries and the development of a prevention program focusing on the trainers, medical professionals and players. Recommendations included structured training, better medical supervision, player reaction time, rule design and enforcement that could result in an overall decrease in injury (170).

The use of controlled head contact with the ball is an important part of soccer. Some would argue that it plays a major role in TBI but this remains a controversial issue (1). It has been shown that older leather balls absorb water and increase the weight of the ball by 20 percent or more making them more dangerous (171). Soccer balls are now made of waterproof synthetic leather covered with urethane which repels water, which has decreased the injury potential (172). Head gear that has been designed to protect players playing soccer has been of limited value (173). A review of the literature has suggested that heading the ball plays a very small part of in soccer related TBI. Instead, accidental unplanned contact against goalposts, head to head contact, elbow contact and a ball kicked directly at the head are more likely to be the source of problems (1, 174). Tysvaer and Storli also noted that the younger players with less experience heading the ball had greater EEG, radiographic and neuropsychological changes than their older more experienced counterparts (162).

Prevention efforts therefore should be directed to better training techniques, proper coaching, adhering to return to play guidelines, medical supervision post injury, rule changes and enforcement. These strategies would minimize unintentional head contact. The use of protective headgear by goalies and development of better head protection would also add to better injury control (172,174).

## HOCKEY

Another sport that can be extremely rough and place the player at a high risk of TBI is hockey (175). Studies have estimated that the range for the incidence of head and neck injuries, excluding facial lacerations, was 6.3 percent to 45.12 percent (176,177). As in football the vast majority of these injuries are concussive in nature. However, in contrast to football, where most injuries occur at the high school level, hockey injuries occur throughout the spectrum of competition; including small children, high school, college and the elite professional teams (178).

The majority of injuries occur during checking, both legal and illegal (179,180). In one study it was found that 57 percent of children with ice hockey related injuries resulted from checking and that more than half of these injuries were considered significant (180). It was also found that the children were not educated on safety and injury prevention as 45 percent of the children reported that they could not sustain a TBI with a helmet on.

Attempts have been made at decreasing injury associated with the game of hockey. There was some thought previously that the use of face masks in hockey players may increase head and neck injuries because the players were more aggressive during play once the mask was on. This has proven to be a fallacy. In one study it was found that there was no significant increase in head and neck injuries with the use of face masks and there was an overall decreased incidence of facial lacerations (181) There have been other reports that mandatory facemasks reduced both facial injuries and TBI (178,182). It has been demonstrated that more hockey injuries occur early in the season, late in the periods and in the final period of games suggesting that conditioning may assist in injury prevention (183).

Education at the younger level is imperative and the emphasis should not be entirely on winning. In one study it was alarming that almost a third of the children would check illegally to win and 6 percent would intentionally injure another player to win (180). Parental attitudes should encourage nonviolence so these behaviors can be learned by their children and taken into adolescence and adulthood.

On the professional level, statistics show that in the Stanley Cup Finals the team with the least penalties secondary to violent behavior win the majority of the series (184).

In summary, sport related injuries account for a significant number of head injuries, which can be severe, fatal, result in long-term debility and/or be the cause of the termination of a player's career. It is important to stress a multifaceted approach to prevention of injury including education, rule enforcement, improvement in safety equipment and better-conditioned athletes with encouragement of nonviolent behaviors.

## VIOLENCE AND SUICIDE

Violence in the United States is a major cause of morbidity and mortality and the statistics raise a significant amount of concern. The fatalities in children and adolescents from firearms have increased from an estimated 3000 fatalities per year in the mid-1980's to 4500 fatalities per year in 1992 (118). Approximately 73 percent of people who sustained a gunshot injury die at the scene, 12 percent die within three hours and 7 percent die after three hours (185). It has been estimated that 90 percent of all persons who sustain a gunshot wound to the head die (186). Upon review of the literature, self-inflicted injuries range from 11–50 percent, with an unclear percentage being accidental (187,188). There are strong demographic factors that contribute to firearm mortality (189). There is a reported tenfold higher rate of homicide in black males related to firearms between the ages of 15 to 19 years old when compared to white males in the same age group (118).

## GUN CONTROL

Handguns continue to be purchased and remain in many American homes. They contribute to a significant amount of morbidity and mortality in the United States annually. Depending on the specific region, it has been estimated that between 15.7 percent and 30.1 percent of all homes contain a handgun (190,191).

Dresang evaluated gun deaths in urban and rural areas and it was found that in rural areas there was a higher amount of shotgun and rifle injuries with handguns accounting for more than 50 percent of gun deaths (192). Those who own handguns are twice as likely to have their gun loaded than an owner of any other type of firearm (193). Homicide risk is increased by threefold and suicide by fivefold among those with a gun in the home (194,195).

It still remains controversial how to enforce handgun control. There have been attempts at legislation, education and safety devices. However more strict regulation is warranted. For example, sales of firearms at gun shows still occur outside of the realm of regulation (196). It is important to realize that more legislation may not meet

that much resistance from the general public. In one report, a large percentage of the public (68 percent) would support government regulation of handgun safety (197). Some believe that only the power of litigation will result in better prevention (196). Past legislation has proven to have a positive effect on injury control. One report noted that a 2-week ban on handguns in parts of Columbia was associated with a reduction in homicide rates in those cities (198). There was also a reported decrease in the number of accidental and home deaths in Maryland after handgun legislation was enacted in Maryland in 1987 (118).

## GUN SAFETY

There continues to be a significant portion of the public that wants to keep a handgun in their homes. In one survey, 29 percent of respondents felt that owning a gun made their homes safer (199). Education of the public should be one of the major components of our preventative measures regarding handgun related injuries. Community based education programs have had some success in encouraging proper storage of firearms (200).

Different technological approaches have been tried to improve handgun safety. Safety locks (trigger lock being the most common), manual thumb safeties, loaded chamber indicators and magazine disconnectors are all attempts to prevent unintentional injuries (201). However, these devices do not protect from intentional injuries such as suicide or homicide. A grip safety feature is a passive preventative method designed to protect children from using the gun. Young children do not have the strength, coordination or hand size to press the safety lever and pull the trigger at the same time. Personalized handguns, a new developing technology, allow only the authorized owner to use the gun. Its features include a built-in locking system and the ability to recognize the authorized user. There are still some concerns regarding its use such as reliability, maintenance and cost. However there is a strong public desire for legislation requiring handguns to be personalized (197). There is no real possibility of an immediate answer to the issue of gun related violence. Zakcos has noted that only legislative lobbying has been linked to organizational resources (202). While Rodriguez stated that only the power of litigation will bring some response to these issues (196).

## OTHER SOURCES OF VIOLENT INJURY

Violence continues to be a major contributing factor to TBI. This continues to be a major concern in urban areas. However it must be noted that there is a reasonable amount of violence in rural areas as well. Jagger et al.

evaluated the epidemiology of head injury in the rural area of north central Virginia. It was found that interpersonal violence accounted for 23/100,000 of head injuries in this area. This number was more than half of that seen for falls alone and overall was a fairly large number (13). The highest number of these types of injuries was in the 30–39 age group. Interpersonal violence included injuries with firearms, blunt weapons, knives or battery without a weapon. These other types of injuries are a worldwide problem. Stab wound injuries, for instance, are extremely high in parts of South Africa (203). Blunt trauma specifically can be mostly attributed to fists, baseball bats, bricks and bottles (204). There have been very little in the way of preventative measures and public education to minimize these other sources of injury.

### DEPRESSION, SUICIDE, AND TBI

There have been reports that intentional TBI has been associated with gender, minority status, age, substance abuse and low socioeconomic status, with the most predictive of these variables being minority status and substance abuse (205). Additionally, a major concern is the risk of suicide among those with TBI. It has been estimated that suicide rates in the TBI population are 2.7 and 4 times higher than the general population when matched for age and sex (206). It has been shown that suicide risk is greater among patients with physical illness than among the general population (207). Simpson and Tate identified various factors of suicide risk in TBI outpatients including hopelessness (35 percent), suicide ideation (23 percent) and suicide attempts (18 percent) (208). A study of several disability groups noted 25 percent of patients had major depression and 7.3 percent reported clinically significant suicidal ideation (209).

There is considerable variability in TBI prevention worldwide. Although there is agreement about goals including general knowledge about suicide and development of skills in suicide risk assessment and management, prevention programs have a wide range of variability (210). The length of training programs for those with professionals and nonprofessional backgrounds range from 1 hour to 16 hours (211,212). Instructional materials used include anything from written materials, self-instructional videos to other methods such as didactic sessions. Some suicide preventative programs are broader and include a more general disabled population. If the TBI population is targeted and appropriate intervention occurs early then some suicides may be prevented. Physicians need to identify risk factors such as suicidal ideation, perform further research on other prognostic factors and be able to manage these patients once their risk has been identified. Simpson et al. created a training workshop for suicide assessment and management for staff in a

rehabilitation center in New South Wales. The length of the workshop totaled approximately 5.25 hours of training in one day. There was improved staff knowledge and skills in suicide assessment and management (210). A larger more multifaceted approach is warranted. In addition to staff training including appropriate agency policies and procedures, collection of appropriate funding and involving more community support (213).

### DRUGS AND ALCOHOL

Recreational pharmaceutical agents greatly complicate the problem of TBI. There have been several reports that head injuries and fractures are the two most common alcohol related types of trauma (214). In its white paper released in 1988 the National Head Injury Foundation Substance Abuse Task Force stated, "neither age, nor occupation, nor any other factors place an individual at a greater risk of a TBI than does alcohol" (215). Many factors contribute to alcohol's exacerbation of TBI. First is the fact that a large minority of the consumers of alcohol are heavy consumers. With Kreutzer et al. estimating that 12 percent of American drinkers can be classified as "problem drinkers" (216). In addition to the large numbers of problem consumers, there is the additional problem of greater injury risk (217). The presence of intoxication at the time of trauma admission increased the odds ratio of a repeat trauma admission within the next 2 years, 2.5 times. In 1999 (218), there were 15,786 deaths and 300,000 injuries as a result of alcohol related MVA. Legal intoxication has been reported in up to 51 percent of people involved in TBI while up to 2/3rd have some history of drug or alcohol abuse (219–221). Positive testing for drugs or alcohol as high as 70 percent has been reported (222). While Anderson reported that 51 percent of non-belted passengers had alcohol on board. High School students demonstrated very significant risk tasking behavior in regards to alcohol. It is alarming that over third of high school students would ride with a driver who had been drinking and over 17 percent would drive after they themselves had been drinking (223).

The importance of preventing teenage drinking has been further clarified by the work of Hingson's group (224). They conducted a survey of college students and demonstrated that there was a relationship between getting drunk for the first time before the age of 19 and drinking and driving, driving after five or more drinks, riding with a driver who was high or drunk and, after drinking, sustaining injuries that required medical attention. In another publication (225) the authors estimated that among college students there were over half a million full-time college students who were unintentionally injured while under the influence of alcohol and over 600,000 assaulted by another student who had been drinking.

Alcohol and drugs can also be involved in other etiologies of TBI. The commencement of drinking prior to age 17 tripled the likelihood that an individual would be involved in a physical fight in the last year (226). A survey performed by Gerhart et. al. demonstrated that alcohol abusers were more likely to sustain a violent TBI as compared to other TBI populations as well as having a worse outcome (227). The incidence of alcohol use in both TBI and SCI patients preinjury is very high. In one report it has been estimated the rate for heavy drinking was 42 and 57 percent respectively (228,229).

There is still some controversy regarding the effect of alcohol on outcomes in the acute setting. Some authors have reported an increased risk of pulmonary complications (230) while other studies have not supported the idea. Cornwell et al. (221). reported that sepsis, complications and mortality were correlated with injury severity and not to the presence or absence of alcohol or drugs. In regards to rehabilitation, Sparedo and Gill (231) reported an association between acute intoxication and lower functional levels at discharge as well as a longer period of post-traumatic agitation. Acute intoxication has also been correlated with longer acute hospitalization and a longer period of posttraumatic amnesia (232). There have also been reports that reported a positive correlation of impaired verbal memory and visiospatial function in those with positive alcohol and drug screens on trauma admission (233,234).

The performance of alcohol screens is not universally performed on all trauma patients (220), with some studies reporting less than 1/2 the trauma patients being tested. This may in part be secondary to a fear of a patient being subject to legal prosecution or denial of insurance coverage if tests are positive. However, this practice is problematic as this hinders both clinical care as well as further research efforts.

While a clear relationship has been established between alcohol and brain injury in the literature, questions still arise as to the most effective means of preventing alcohol related TBI. Prevention efforts must be directed at both passive and active measures as passive efforts alone have had a limited effect. Passive efforts such as breathalyzer testing, mental status or coordination testing prior to starting a car has been discussed for years but have not become a reality. Another intervention, that is passive to the alcohol consumer is the modification of the server's behavior. This is part based on the concept that many people who drink and drive are consuming alcohol at bars, clubs and restaurants (218). It has been reported that about half of the people who received a DUI left a place that served alcohol (235, 236). Efforts that focus on educating servers to carefully screen underage drinkers, refuse service to rapid drinkers, calling taxi services for consumers that seem unfit to drive and the offering of food to those drinking are all ways to delay potential intoxication and

driving under the influence. Currently there is no uniformity between the educational programs across the country with some states having mandatory programs, while others voluntary educational programs for servers. The programs are not standardized across the country and address different issues such as legislation regarding intoxication, DUI, recognizing the signs of intoxication as well as liability issues. The fear of litigation may assist the management structure of these establishments to be supportive of their employees' efforts to mitigate this national problem and run a safer establishment (218).

These programs have been proven to be effective in both improving servers' decision making abilities (237) and in decreasing patrons' level of intoxication (238–240). Holder et al. (241). demonstrated that using these measures in three experimental communities resulted in a 10 percent reduction in alcohol related traffic accidents and significantly reduced the sale of alcohol to minors. These interventions have been shown to only be effective for about a year with some drop off after 15 months (242). It is therefore important to recognize the need for continuing education, which may be needed on a yearly basis. Mandatory legislation is still warranted for continuing education targeting servers.

Significant progress has been achieved due to alcohol related prevention programs. Since 1982, the rate of alcohol related MVA fatality has steadily dropped from a rate of 57 percent to 38 percent (218). Zobeck et al. also reported similar findings with a 10 percent decrease in alcohol related MVA fatalities from 1979–1990 (243). Not only that, but fatality rates per 100 million vehicles miles traveled, and per 100,000 population, registered vehicles and licensed drivers have decreased even more sharply. This may be due the multifaceted approach of various interventions such as public education, community programs, legislation and enforcement.

Recently, The Internal Medicine News has reported about the decrease in the use of alcohol and illicit drugs in the young. Kirn reported results of a national survey that questioned 50,000 students that were attending either public or private schools regarding their usage of illicit drug within the previous month. It demonstrated a 7 percent decrease in illicit drug use from 2003 to 2004. In addition he reported an overall decline in drug use over the past three years among high school seniors and the last eight years for younger teens (244). Jancin reported on the potential value of early recognition of young children who are at risk for developing problems with substance abuse later in life; in particular, evaluating preschoolers for the presence of temperament traits such as aggressiveness, impulsivity, poor attentiveness. Once these "red flags" are identified, some suggest that early comprehensive psychological evaluation with early intervention may help reduce the risk of problems later on in the teen and adolescent years (245)

Community programs such as Mothers Against Drunk Driving (MADD) have been instrumental in having the legal drinking age raised to 21 throughout the United States (21). However, raising the legal drinking age to 21 has not totally eliminated alcohol as a problem for teenage drivers. Alcohol has clearly been found in adolescents involved in trauma (246). In 1997, 21 percent of those killed driving while driving intoxicated were 15–20 years of age (120). In addition, 41 percent of college students report episodes of binge drinking during the previous 2 weeks (247). Control of access clearly is not enough to address the problem of alcohol related MVA.

Active preventative measures have been suggested to prevent TBI. Previously suggested strategies include involving survivors in policy making, working with journalists to improve media coverage of head injury and speaking to high-risk groups to encourage use of protective gear (248). Although all survivors cannot participate in every domain suggested, simple tasks associated with office maintenance, for example, could still contribute to head injury prevention. It is therefore important to channel the brain injury community to programs that facilitate education, legislation, public policy, lobbying, advertising and media, all aspects of prevention that need to be addressed by both survivors and health care professionals (214).

Preinjury family dynamics must be addressed after a TBI. A brain injury may magnify a dysfunctional family structure. There must be strategies for the family to learn how to cope with substance abuse and brain injury. This may help prevent a second injury or repetitive abuse behavior (219). The family must be involved in collaborative approaches between the health care provider and abuser. There must be consistent use of support groups with family participation. The family must be educated on the risk factors for abuse as well as be provided with coping mechanisms on how to handle and separate TBI related issues from abuse issues.

It is estimated that there are over 1.4 million DUI arrests every year in the United States. While this seems like a large number it is relatively small when it is compared to the number of actual occurrences. There are estimates of up to 126 million episodes of DUI that actually occurs every year in the United States (120). The original threshold for determining that one was driving while intoxicated or under the influence laws was 0.10 grams per deciliter. Evidence arose that even lower levels of blood alcohol could impair one's driving ability and in 1983 Utah and Oregon were the first two states that lowered the level to 0.08 grams per deciliter. By May 2001 24 states had lowered the acceptable blood alcohol level to less than 0.08 gm/deciliter for drivers 21 years of age (218). For those 20 and under a zero tolerance policy was adopted and any evidence of blood alcohol is considered illegal and subject to legal sanction (218,249).

Several studies have addressed the impact of this lowering of acceptable blood alcohol levels (250–258), which have been reviewed by Shults et al. (218). As a result of these changes, the overall rate of alcohol related MVA fatality dropped by 7 percent. In California and some of the other states, immediate confiscation of licensure, called administrative license revocation (ALR) was also implemented. In an effort to isolate the effects Hingson et al. looked at the effect of the BAC change in states which already had ALR rules on the books and noted a 5 percent decrease in alcohol related fatalities when the lower BAC rule was instituted (253). Voas et al. used a statistical approach to separate the different factors. Using multivariate analysis he demonstrated that there was a reduction of 8 percent in alcohol related fatalities as a result of lowering of the acceptable BAC level by itself (258). There are great cultural, demographic and geographical differences between the states studies so it is assumed that the results of these studies are likely to be representative of the United States (218). The U.S. Congress has been impressed enough by the evidence to require all states to lower the BAC to 0.08 gm/dl by October 2003 or they will lose federal highway funds (259).

Younger drivers, partake in other risk taking behaviors and are at greater risk of MVA than their more experienced counterparts. This may be a result of decreased experience or partaking in other risk taking behaviors that are associated with alcohol ingestion. The work of Anderson et al. that demonstrated that over half of non seat belt wearing drivers involved in a MVA were positive for alcohol as compared to 22 percent of those wearing shoulder belts serves as an example (260). Similarly, there is a much lower use of restraints among those who ingest alcohol. This is especially true with adolescents where only 7 percent with positive alcohol screens were using a restraint system as compared to 22 percent that had no alcohol (246). While, Peek-Asa and Kraus (88) demonstrated that motorcyclists involved in accidents who tested positive for alcohol were more likely to be speeding and not be wearing a helmet. Finally, Zador et al. (261) demonstrated that a 16 to 20 year old male who had a BAC level between 0.08 and 0.1 had a 24 times greater chance of dying from a MVA as compared to a BAC of zero. The benefit of Congressional mandates was again noted when its threat to withhold highway funding, prompted all states to pass legislation that requiring a BAC level of less than 0.02 for all drivers under 21 years of age (220). The minimum drinking age was first raised to 21 in several states by the 1970s. By 1987, all 50 states had raised the minimum drinking age to 21 (218). As a result of this change a double-digit decrease in both fatal and non-fatal MVA's was noted.

Legislation requires enforcement to be effective. There is a need to improve these efforts to facilitate prevention efforts. Sobriety checkpoints are an effective



means of addressing this issue. There are two types of sobriety checkpoints, random breath testing (RBT) and selective breath testing (SBT). RBT has been used with Australia and Europe with great benefit. It is not currently available in the United States because of a lack of "probable cause." Instead in the United States only SBT sobriety checkpoints are utilized. With SBT checkpoints, the officer must have reasonable suspicion of intoxication in order for breath testing to be performed. Because of the nature of these checkpoints, they better serve the purpose of deterrence rather than actual identification of offenders (218).

SBT checkpoints have proven their efficacy and have been shown to reduce fatal car crashes 20–26 percent (262), as well as reducing overall crashes anywhere from 5 to 23 percent (218). RBT has been tested and has shown similar results (263–271). The studies of RBT showed a reduction in fatal crashes between 13–36 percent (264, 268, 269, 271) and 11–20 percent for all crashes (263, 265–271). RBT has also been shown to modify drivers' behavior in regards to drinking and driving. Work from Australia reported a 13 percent drop in drivers with any detectable alcohol on board and a 24 percent decrease in BAC level over 0.08 with RBT (223). The literature has shown that both the selective and random method of testing has been useful in reducing crashes of all types. While RBT is more sensitive than SBT relative to detecting elevated BAC, the literature has not demonstrated any difference in efficacy between the two methods relative to crash prevention (218). Technologic breakthroughs such as the addition of passive sensors that can sample for the presence of alcohol are being developed which may further increase the sensitivity of SBT by 50 percent which will further increase the sensitivity of SBT (272).

Even with proven efficacy, these programs face resistance as a possible violation of an individual's civil rights. The United States Supreme Court has weighed in and ruled on the appropriateness of a properly performed brief sobriety check. The sense of the court was that this minor intrusion on human rights was more than balanced out by the public benefit of reducing DUI (273). Cost benefit issues is another issue raised regarding the use of SBT and the cost benefit ratio of having police officers man these checkpoints. Miller et al. (274), have addressed this issue. In their model of a community of 100,000 licensed drivers and assumed that the intervention would reduce accidents by 15 percent, a number chosen after reviewing the literature on SBT. Incorporating all of the costs of alcohol related MVA including medical, property etc, and their estimates were that \$9.2 millions would be saved with an expenditure of \$1.6 million with a ratio of nearly 6 to 1. An actual study performed in California was even more promising. Four communities introduced SBT for over ninth months at a relatively small cost of \$165,000. The savings that resulted from this intervention resulted

in a 23 times as large a benefit of \$3.86 million. RBT testing may be more effective than SBT financially. Work from Australia and New South Wales has suggested that at an annual cost of \$4 million per year a savings of \$228 million was realized as a result of accident prevention (264). The efficacy of these programs both from a financial as well as from crash prevention requires society to take a look at these papers.

## PEDIATRIC HEAD TRAUMA

Pediatric injuries are a significant cause of morbidity and mortality throughout the world. Approximately 600,000 children are hospitalized every year and more than 15 million children are seen in the emergency room each year because of their injuries (116). Head trauma accounts for over 500,000 emergency department visits annually (275). The annual costs exceed over 1 billion annually and 29,000 children sustain permanent disabilities.

## CHILD ABUSE

Homicide from child abuse is the leading cause of death in infants in the United States (118). In 1999, approximately 4.1 percent of children less than 18 years old were victims of physical, emotional or sexual abuse (276). In a survey of pediatric head trauma, abuse accounted for 19 percent of cases and was associated with a higher rate of subdural hematoma (SDH), subarachnoid hemorrhage, as well as retinal hemorrhages (277). Child abuse is not only a form of violence but contributes to adverse consequences in maltreated children. Abuse in childhood has been associated with early pregnancy, drug abuse, school failure, mental illness, suicidal and aggressive behavior and violence later in life. Center (276).

Shaken baby syndrome results from severe movements of a child's head, can result in retinal hemorrhages, cerebral axonal injury, occult cervical injury, and coagulopathy (278, 279). Young infants have weak neck muscles leaving them vulnerable to sustain SDH and shearing injuries. For a retinal hemorrhage to occur, it takes an extraordinary force and is usually not associated with an accidental injury (280). There are many educational programs in place to educate the community of the severe danger of shaking infants.

Child abuse has been associated with single-parent homes, low-income families and parents with alcohol and drug abuse and many home visitation programs in the United States are therefore directed toward these high risk populations. The Center of Disease Control and Prevention noted that preventative programs delivered by nurses demonstrated a median reduction in child abuse of 48.7 percent and programs delivered by mental health

workers demonstrated a median reduction in child abuse of 44.5 percent (276). In one study sample evaluating the cost-benefit ratio of home visits to low-income mothers, there was a net benefit of \$350 dollars per family in 1997. Clinicians should also continue to target high-risk populations such as teenage parents, single mothers, families of low socioeconomic status and parents with alcohol, drug or mental health problems. Further programs are warranted to reach the goal of reduction of homicides from 6.5 to 3.0 per 100,000 populations by 2010 (281).

### **CAR SEATS AND AIR BAGS**

Motor vehicle accidents are the major cause of death in children and adolescents. It has been estimated that motor vehicle accidents and traffic-related injuries account for 56 percent of injury fatalities (118), with front seat passengers appearing to be at the highest risk. There was legislation early on in the 1990's that focused its attention on placing young children in the back seat in addition to standardized three point restraints in all vehicles. The 1990s saw a decline in front seating of children in vehicles involved in fatal crashes likely attributed to public awareness and education and legislation (282). However children ages 6 to 12 remained at high risk for being front seated (282). Pediatric air bags systems pose a threat to the front-seated child passenger, with resultant cranial and cervical spine trauma (79). Patterns of injury in the child or adolescent will be different than that for an adult given the seat location, height and weight of the individual type of restraint and the biomechanics at impact placing the child closer to the deploying air bag all have an effect (283). Both age and weight of the child determine the appropriate restraint system. There has been legislation regarding child restraint system utilization, however, the poor compliance with these devices is concerning (284).

It has been estimated that 500 deaths and 53,000 injuries could be prevented each year if there were 100 percent compliance with existing state law and there was proper use of child safety belts (118). It is encouraging that education and legislation, including passive and active strategies, can result in a decrease in childhood injury.

### **PLAYGROUND AND RECREATIONAL INJURIES**

In 1986, the United States Consumer Product Safety Commission estimated that approximately 7,000 children under the age of 15 had sustained a playground related injury that required hospitalization (116). Between 1990–1994, more than 200,000 playground injuries were reported (285). It has been estimated that 8 percent of

sport and recreation related head injuries are playground related (286).

A large proportion of injuries are related to climbing activities including monkey bars, jungle gyms, swings and slides, with approximately 25 percent of such injuries requiring hospitalization (287). In one study of Boston's playgrounds, 34 percent of playground hazards were related to climbers, 30 percent with slides and 22 percent with swings (288). Lillis & Jaffee evaluated all children injured on playground equipment in a metropolitan center in Canada. It was found that 39 percent of the children were under age 5 and 58 percent of those younger than 5 years old had head and cervical injuries (116).

Lessening the incidence and consequences of falls from playground equipment is a promising potential target for prevention efforts (289). Multifaceted efforts are important. Parents need to be educated and provide appropriate supervision in the playground environment. One study suggests one of the main contributing factors to playground injury is "lack of active competent adult supervision." (290) Educating children not to jump off a moving swing or walk behind a moving swing must be reinforced to the parents. The use of equipment by older children designed for younger children such as certain slides and climbing equipment that are very narrow can be dangerous. As a result the older child may slip or fall. Some slides are elevated 10–15 feet off the ground and the danger of the slide increases with increasing height. Unfortunately, the drive for safer design of playground sites has been pushed more by litigation than public policy.

The riding bicycles by children is another important area for prevention efforts and the use of helmets during bicycle riding is critical. It has been estimated that wearing helmets resulted in a 88 percent less risk of brain injury compared to those people who did not wear helmets (149). The problem is that use of helmets by North American children is less than 1 percent (146). This may be because children may feel like they do not fit in with their peers. If so, this is a strong reason to make helmet use mandatory and legislation is warranted to mandate helmet use in children. Legislation in addition to education of parents and children may improve compliance with helmet use. Skateboards are a common source of head injuries in the pediatric population. It appears that the rate of injury secondary to skateboards has surpassed that of bicyclists for those under 25 (291). The role of helmets in preventing serious injury related to skateboarding is also critical.

### **CONCLUSION**

Traumatic brain injury is a major health problem for society. It is an area where prevention efforts can make a substantial difference in the overall public health. Prevention

efforts must be directed at many different components that include legislation, education and motivation of the public to control this area of injury. There has been a tremendous progress made in TBI prevention over the last few decades. However, there is still a large amount of work needed to target all the different aspects, or "cells" in the Haddon Matrix, that contribute to TBI. Health care providers must continue to educate the lay public and assist politicians in recognizing the benefits of injury control. Hopefully as public awareness, technology and legislation improve so will prevention efforts.

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# 8

## TBI: Pathobiology

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### INTRODUCTION

In the United States, over 50,000 people die and over 200,000 are hospitalized each year from traumatic brain injury (TBI) (1). Severe TBI is an important contributor to both this level of mortality and the associated morbidity. Treatment is usually supportive neurointensive care focused on the control of intracranial hypertension. Breakthroughs in the treatment of TBI have been hampered by a lack of understanding of the key mechanisms operating in the injured brain.

TBI involves a primary injury that includes direct disruption of brain parenchyma, and a secondary injury characterized by a cascade of biochemical, cellular, and molecular events involved in the evolution of secondary damage.

### PRIMARY INJURY

Primary injury has traditionally been characterized as the damage that results directly from the shear forces at impact. Consequently, this topic has been of greater interest to investigators in the fields of injury prevention and biomechanics than those focused on the treatment of the evolution of secondary damage. A detailed discussion of the biomechanics of primary injury is beyond the scope of this chapter. Nevertheless, some insight into its

components is valuable. Key components of primary injury include cortical disruption, axonal injury, vascular injury, hemorrhage, and unusual, albeit important, miscellaneous forms of primary injury.

Primary injury has been modeled *in vitro* using approaches such as mechanical stretch of cultured neurons (2). Clinically, a number of aspects of primary injury can be appreciated when viewing the initial post-injury cranial computed tomographic (CT) scan or cranial magnetic resonance imaging (MRI) of patients. Direct cortical disruption seen in the initial minutes to hours after the insult represents primary injury that is not likely to be amenable to resuscitative therapy. In addition to direct cortical disruption, axonal injury and vascular disruption can result from primary injury. Indeed, because it is likely related to the anatomical association between axons and blood vessels, primary injury often results in coupled injury to these structures—and the commonly observed clinical picture of petechial hemorrhages in white matter signaling diffuse axonal injury (DAI) (3).

Classically, axonal disruption with retraction was believed to result only from direct shearing. However, work from the laboratory of Povlishock (4) over the past decade has identified a parallel secondary injury cascade in axons. Thus, as with gray matter injury, both primary and secondary axonal damage can occur after severe TBI. The concept of secondary axonal damage will be discussed in greater detail later in this chapter. Finally, there are a number of

miscellaneous forms of primary injury—and several of these can have critical consequences in the setting of acute injury. For example, pituitary stalk transection from shear forces has been reported (5) and leads to acute pituitary failure. Primary injury to the brain stem can also occur and often is associated with poor outcome (6). Similarly, primary injury from violent shaking in the setting of inflicted childhood neurotrauma (shaken baby syndrome) can include direct shearing of nerve roots in the upper cervical spine (7).

Another important aspect of primary injury is impact depolarization. At the time of severe injury, impact depolarization occurs, with massive increases in extracellular potassium ion and the indiscriminate release of the excitatory neurotransmitter glutamate (8). This immediate event initiates excitotoxicity—a key secondary mechanism that is discussed in detail latter in this chapter.

Although by definition, primary injury is not likely to be responsive to resuscitative approaches; it is interesting that our thinking on the lack of therapeutic approaches to primary injury may require reconsideration in the emerging era of tissue engineering and stem cell therapeutics (9). It is possible, that tissue replacement therapy in the future may allow successful therapeutic avenues even to lesions produced by primary injury and previously felt to lack therapeutic options. This could be particularly important as an adjunctive therapy in rehabilitation.

### EVOLUTION OF SECONDARY INJURY

Secondary injury includes both the endogenous evolution of damage within the brain and the effects of secondary

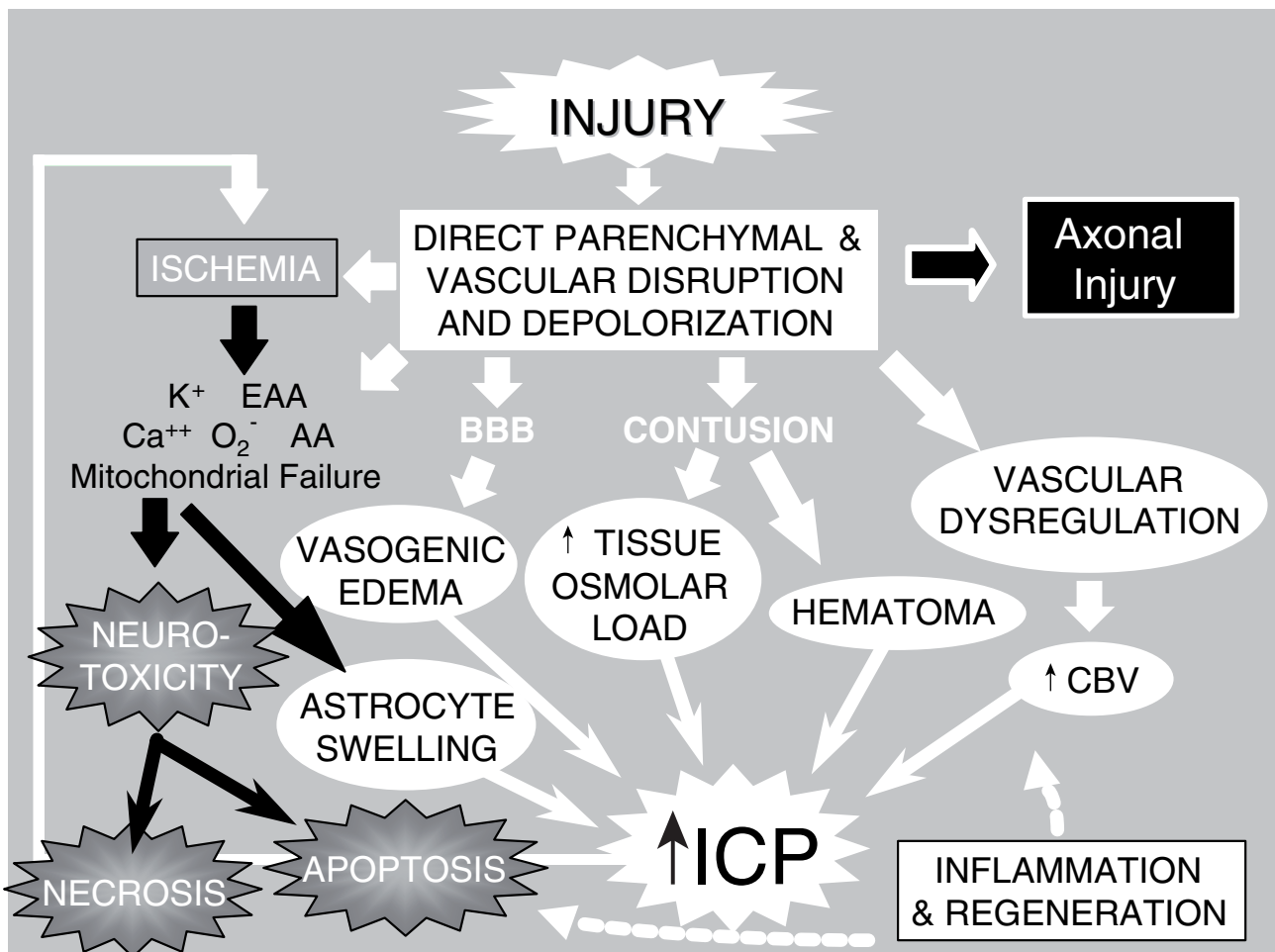


FIGURE 8-1

Categories of mechanisms proposed to be involved in the evolution of secondary damage after severe TBI in infants and children. Three major categories for these secondary mechanisms include (i) ischemia, excitotoxicity, energy failure, and cell death cascades; (ii) cerebral swelling; and (iii) axonal injury. A fourth category, inflammation and regeneration, contributes to each of these cascades.  $K^+$  = potassium; EAA = excitatory amino acids;  $Ca^{++}$  = calcium;  $O_2^-$  = superoxide; AA = arachidonic acid; BBB = blood brain barrier; ICP = intracranial pressure; CBV = cerebral blood volume

extra-cerebral insults (i.e., hypotension, hypoxemia) from the injury scene through the intensive care unit (ICU).

Studies in models of TBI have begun to unravel the mechanisms producing secondary damage. Four categories of mechanisms can be defined (Figure 8-1), those associated with (i) ischemia, excitotoxicity, energy failure, and resultant cell death cascades; (ii) secondary cerebral swelling; (iii) axonal injury; and (iv) inflammation and regeneration. Within each category, a constellation of mediators of secondary damage, endogenous neuroprotection repair, and regeneration are involved. The quantitative contribution of each mediator to outcome and the interplay between these mediators remains poorly defined.

A variety of methods have been used to study the evolution of secondary damage in human head injury including (i) the analysis of brain biochemistry and molecular biology via of ventricular cerebrospinal fluid (CSF) drained in the treatment of intracranial hypertension, (ii) assessment of brain interstitial fluid by cerebral microdialysis, (iii) imaging techniques linked to assessment of cerebral blood flow (CBF) and cerebral metabolism, and (iv) the assessment of molecular markers in brain tissue obtained from patients treated with surgical decompression for refractory intracranial hypertension. We discuss these studies and cite the clinical evidence supporting proposed mechanisms of secondary damage. It is impossible to address all of the mediators that may be involved; however, key mechanisms will be considered.

## POST-TRAUMATIC ISCHEMIA

Clinical studies in adults have indicated that soon after severe TBI, CBF is reduced and suggest that early post-traumatic ischemia might represent a therapeutic target (10,11). Clinical studies applying the stable xenon computed tomographic (CT) method of CBF assessment in the initial hours after severe TBI have been the most important in this regard. Early hypoperfusion or ischemia after severe TBI appears to represent a finding that is seen in most cases and is associated with poor outcome. The devastating consequences of secondary extra-cerebral insults early after injury (i.e., hypotension, hypoxemia) early post-trauma are also consistent with this possibility—because a hypoperfused brain is at high risk and may be incapable of mounting an appropriate vasodilatory response during these added insults (12). This is not to suggest that secondary insults are limited to the field or emergency department. Secondary ischemic insults can also occur in the ICU. This was best described in the classic report of Gopinath et al., (13) who used a jugular venous catheter to identify episodes of jugular venous desaturation ( $SjvO_2 < 50$  percent for more than 10 minutes) in the ICU in 116 patients with severe TBI. In that study, 46 of the 116 patients had at least one episode of

desaturation—suggesting ischemia. The causes of these episodes were either systemic such as hypotension or cerebral such as refractory intracranial hypertension. Episodes of desaturation were strongly associated with a poor neurological outcome. Just a single desaturation increased the incidence of poor outcome from 55 percent to 74 percent.

Numerous mechanisms may underlie the early post-traumatic hypoperfusion. Armstead reported reductions in the vasodilatory response to nitric oxide (NO), cGMP, cAMP, and prostanoids after experimental TBI in pigs, along with the release of superoxide anion (14,15). Also, greater injury-induced release of the potent vasoconstrictor peptide endothelin-1 in the newborn versus the juvenile pig was posed to mediate the hypoperfusion (16). Others have suggested a loss of either endothelial NO production, or reduced responsivity to NO as mediating hypoperfusion. Treatment with L-arginine (the substrate for NO production) improved CBF after TBI in rats (17). Similarly, treatment with L-arginine improved CBF and reduced contusion volume after TBI in rats (18). L-arginine is being tested in a clinical TBI trial in adults (personal communication, C. Robertson, MD). Loss of vasodilators and elaboration of vasoconstrictors, or other mechanisms, might be involved in producing early post-traumatic hypoperfusion (Figure 8-2).

Increases in metabolic demands, related to uptake of glutamate, as reflected by increases in brain tissue and CSF lactate, early after TBI have been reported in both models (19) and humans (20–22). Thus, reduced metabolic demands with a coupled CBF reduction in severely injured brain regions, early after injury, is an unlikely explanation for the hypoperfusion.

At more delayed times after injury (several hours to days), oxidative metabolism has been noted to be reduced to levels of ~50 percent of baseline for the

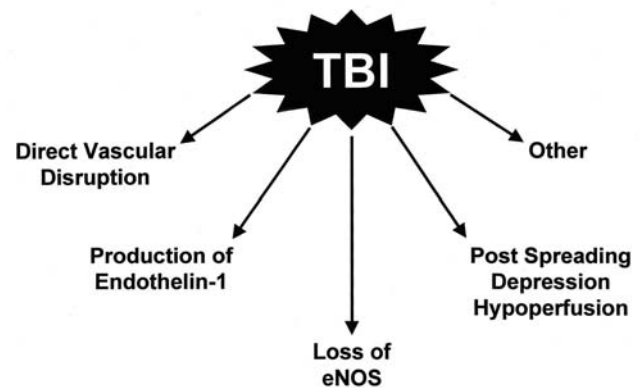


FIGURE 8-2

Schematic outlining putative mediators involved in the production of early post-traumatic hypoperfusion and/or ischemia after severe TBI. NOS = NO synthase. (See text for details.)

majority of the ICU course (20). The complex issue of issue alterations in metabolic demands after severe TBI is discussed in greater detail in the section on brain swelling later in this chapter.

### EXCITOTOXICITY

Excitotoxicity describes the process by which glutamate and other excitatory amino acids (EAAs) cause neuronal damage. Lucas and Newhouse (23) first described the toxicity of glutamate. Olney (24) subsequently reported that intraperitoneal administration of glutamate produces brain injury. Although glutamate is the most abundant neurotransmitter in the brain, exposure to toxic levels produces neuronal death (25).

Glutamate exposure produces neuronal injury in two phases. Minutes after exposure sodium-dependent neuronal swelling occurs (26). This is followed by delayed,

calcium-dependent degeneration. These effects are mediated through both ionophore-linked receptors, labeled according to specific agonists (N-methyl-D-aspartate [NMDA], kainate and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA]), and receptors linked to second messenger systems, called metabotropic receptors. Activation of these receptors leads to calcium influx through receptor-gated or voltage-gated channels, or through the release of intracellular calcium stores. Increased intracellular calcium concentration is the trigger for a number of processes that can lead to cellular injury or death (Figure 8-3). One mechanism involves activation of constitutive NO synthase, leading to NO production, peroxynitrite formation and resultant DNA damage. Poly(ADP-ribose) polymerase (PARP) is an enzyme operative in DNA repair, and in the face of DNA damage, PARP activation leads to ATP depletion, metabolic failure and cell death (27). This may be important since PARP knock-out mice exhibit improved outcome versus controls (28).

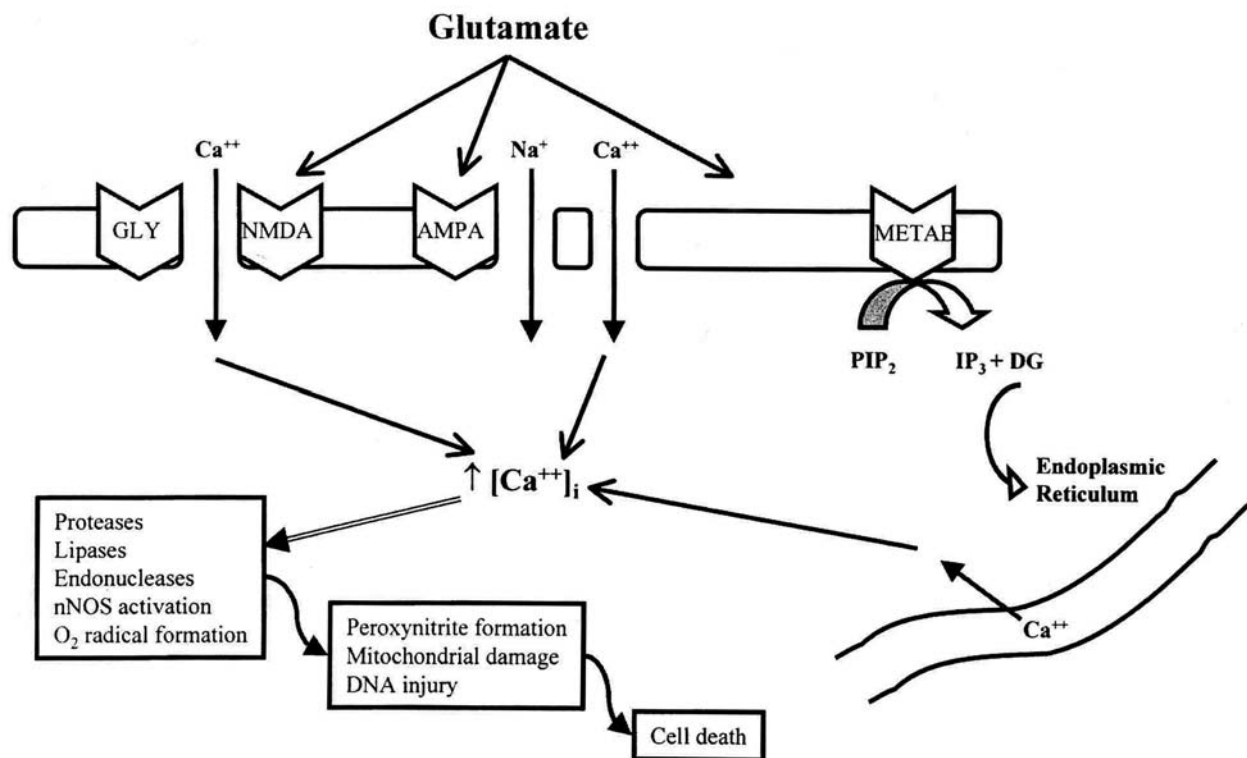


FIGURE 8-3

Mechanisms involved in excitotoxicity. Glutamate causes an increase in intracellular calcium concentration through stimulation of (i) the NMDA receptor with opening of the receptor-linked calcium ionophore, (ii) the AMPA receptor with opening of the voltage-gated calcium channels, and (iii) the metabotropic receptor, with the release of intracellular calcium stores via the second messengers inositol triphosphate and diacylglycerol. Increased intracellular calcium concentration leads to activation of proteases, lipases and endonucleases, along with neuronal NOS stimulation and production of oxygen radicals. This results in peroxynitrite formation, mitochondrial damage and DNA injury with subsequent cellular injury and death.

*Abbreviations:* GLY: glycine coagonist site; NMDA: N-methyl-D-aspartate receptor; AMPA:  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor; METAB: glutamate metabotropic receptor; PIP<sub>2</sub>: phosphoinositide; IP<sub>3</sub>: inositol triphosphate; DG: diacylglycerol

Recent evidence suggests that activation of PARP within mitochondria may contribute importantly to their failure (29).

Faden et al. (30) first reported an increase in interstitial EAAs to neurotoxic levels after experimental TBI. Anti-excitotoxic therapies improve outcome after experimental TBI. Pretreatment with NMDA antagonists (phencyclidine, MK-801) attenuate behavioral deficits after TBI in rats (31, 32). Other therapies that modify the glutamate-NMDA receptor interaction and improve outcome following experimental TBI are magnesium (33), glycine site antagonists (34), hypothermia (35), and pentobarbital (36).

Palmer et al. (37) first demonstrated increased concentrations of EAAs in ventricular CSF from adult patients with TBI. Glutamate concentrations were about 5-fold greater than in control patients (up to 7  $\mu\text{M}$ )—levels sufficient to cause neuronal death in cell culture (38). However, CSF glutamate concentrations do not correlate to outcome after TBI in adults (39). Bullock et al. (40) characterized patterns of glutamate release by measuring EAAs by microdialysis after adult TBI. Patients with a normal head CT and no secondary ischemic events had interstitial concentrations of glutamate that were increased early in their course, then returned to normal, similar to the pattern seen in most experimental models. A second group of patients had an intermediate increase in glutamate concentration (5–20  $\mu\text{M}$ ) that declined over time, but remained higher than normal. Most of these patients had ischemic events or intracranial hypertension. A third group of patients had markedly increased concentrations of glutamate (over 20  $\mu\text{M}$ ). All patients with a progressively rising level of glutamate died.

Despite these findings, clinical trials with anti-excitotoxic therapies have been unsuccessful. This may be due to the fact that most therapies have been applied to all patients with TBI rather than those with excitotoxicity (41). Also, treatment may have been initiated too late. Inhibition of plasticity by anti-excitotoxic therapies may limit their efficacy—especially at the interface between the acute and subacute periods after injury (42).

## ENDOGENOUS NEUROPROTECTANTS

Ischemia, excitotoxicity, or their combination is a key facet of secondary injury. These mechanisms are linked to calcium overload, oxidative stress, and mitochondrial failure. Studies have begun to define, in infants and children with severe TBI, the endogenous retaliatory response to these ischemic and excitotoxic insults. Space limitations have directed us to focus on two examples of this cascade—namely, adenosine and heat shock protein 70 (HSP 70). Endogenous neuroprotective responses related to the apoptosis, cell signaling, and inflammatory cascades are discussed later.

Adenosine is an endogenous neuroprotectant produced in response to both ischemia and excitotoxicity. Adenosine antagonizes a number of events thought to mediate neuronal death (43). Breakdown of adenosine triphosphate (ATP) leads to formation of adenosine, a purine nucleoside that decreases neuronal metabolism and increases CBF, among other mechanisms. Adenosine binding to A1 receptors decreases metabolism by increasing  $\text{K}^+$  and  $\text{Cl}^-$  and decreasing  $\text{Ca}^{++}$  conductances in the neuronal membrane. A1 receptors are located on neurons in brain regions that are susceptible to injury (i.e., hippocampus) and are spatially associated with NMDA receptors (44). Thus, released adenosine minimizes excitotoxicity. Binding of adenosine to A2 receptors (on cerebrovascular smooth muscle) causes vasodilation, although binding to A2a receptors on neurons may be detrimental. Brain interstitial levels of adenosine are increased early after TBI in rats (45–47). In experimental TBI, brain interstitial adenosine increases immediately after injury to levels 50- to 100-fold greater than baseline (47). In clinical studies, marked increases in brain interstitial levels of adenosine in adults with TBI, were seen during episodes of jugular venous desaturation (secondary insults), supporting a role of adenosine as a “retaliatory” defense metabolite (48).

Another putative endogenous neuroprotectant that plays a role after severe TBI is HSP 70. This protein is induced as part of the classic preconditioning response in brain and has recently been shown to be increased in both CSF and brain tissue after severe TBI in humans (49–51). HSP 70 is believed to play an important role in optimizing protein folding as a molecular chaperone. It also inhibits pro-inflammatory signaling (52). Thus, the brain mounts an important endogenous defense response to TBI. Therapies designed to augment these pathways have not been examined adequately.

## APOPTOSIS CASCADES

It is now increasingly clear from experimental models and human data that cells dying after TBI can be categorized on a morphological continuum ranging from necrosis to apoptosis (53,54). Apoptosis is a morphological description of cell death defined by cell shrinkage and nuclear condensation, internucleosomal DNA fragmentation, and the formation of apoptotic bodies (55). In contrast, cells dying of necrosis display cellular and nuclear swelling with dissolution of membranes. Apoptosis requires a cascade of intracellular events for completion of cell death; thus, “programmed-cell death” is the currently accepted term for the process of cell death that leads to apoptosis (56). In diseases with complex and multiple mechanisms, such as TBI, it is typically difficult to distinguish clinical apoptotic vs. necrotic cell death as classically defined (57).

Some cells may display DNA fragmentation and activation of proteases involved in programmed-cell death, despite having nuclear and cellular swelling. Dying cells with mixed phenotypes may represent particularly difficult therapeutic targets after TBI.

In mature tissues, programmed-cell death requires initiation via either intracellular or extracellular signals (see Figure 8-4). These signals have now been well characterized *in vitro*, and are becoming better characterized *in vivo*. Intracellular signaling appears to be initiated in mitochondria, triggered by disturbances in cellular homeostasis such as ATP depletion, oxidative stress, or calcium fluxes (58). Mitochondrial dysfunction leads to egress of cytochrome c from the inner mitochondrial membrane into the cytosol. Cytochrome c release can be blocked by anti-apoptotic members of the bcl-2 family (e.g., bcl-2, bcl-xL, bcl-w, and Mcl-1), and promoted by pro-apoptotic members of the bcl-2 family (e.g., bax, bcl-xS, bad, and bid) (59).

Cytochrome c in the presence of dATP and a specific apoptotic-protease activating factor (Apaf-1) in cytosol activates the initiator cysteine protease caspase-9 (60). Caspase-9 then activates the effector cysteine protease caspase-3, a key apoptosis effector that cleaves cytoskeletal proteins, DNA repair proteins, and activators of endonucleases (61).

An additional intracellular cascade of programmed cell death linked to mitochondrial injury is the apoptosis-inducing factor (AIF) pathway (62–66). This caspase-independent pathway is activated by mitochondrial permeability transition and results in the release of AIF from the mitochondrial membrane. AIF release leads to large-scale DNA fragmentation (50–700 kilo-base-pair in size). Recently, Zhang et al. (67) reported that the AIF pathway is activated in experimental TBI. To date, specific pharmacologic inhibitors of this pathway are lacking, however, this alternative form of delayed neuronal death may represent an important therapeutic target.

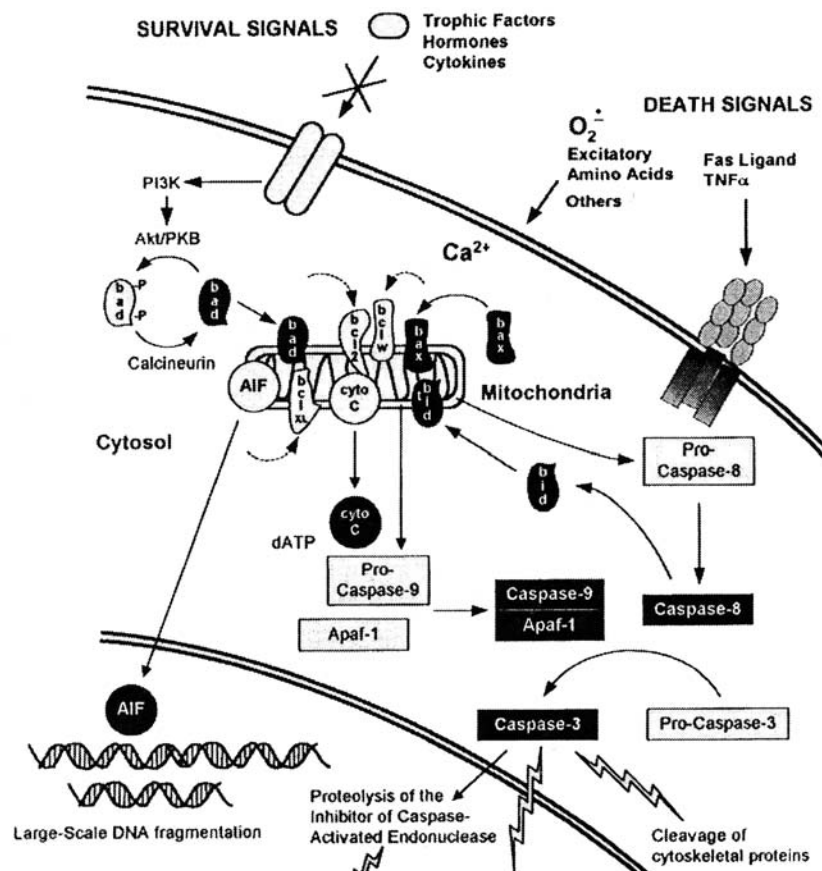


FIGURE 8-4

Simplified schematic depicting intracellular and extracellular pathways for programmed-cell death. Mitochondrial dysfunction caused by injurious stimuli such as oxidative stress or calcium fluxes can trigger release of cytochrome c or apoptosis inducing factor (AIF). Cytochrome c in the cytosol along with other enzymes and cofactors initiates activation of a cascade of caspases, culminating in apoptotic DNA cleavage. AIF triggers caspase-independent large-scale DNA fragmentation (see text for details). Programmed cell death can also be initiated by cell death receptors on the cell surface. Fas-ligand (Fas-L), either presented by an effector cell or in soluble form, binding to Fas-receptor (Fas-Rc), or TNF binding to TNF-receptor (TNF-Rc), can also initiate a cascade of caspases via intracellular death domains

Extracellular signaling of apoptosis occurs through the TNF superfamily of cell surface death receptors which include TNFR1 and Fas/Apo1/CD95 (68). Receptor-ligand binding of TNFR1-TNF $\alpha$  or Fas-FasL promotes formation of a trimeric complex of TNF- or Fas-associated death domains, respectively. These death domains contain caspase recruitment domains. The proximity of multiple caspases, in this case caspase-8, allows for activation of the effector cysteine protease followed by activation of caspase-3, where the mitochondrial- and cell death receptor-pathways converge. The cell death receptor pathway can also be regulated by soluble receptors and ligands that prevent and promote apoptosis, respectively, and by receptors lacking death domains. Finally, there is cross-talk between mitochondrial- and cell death receptor-pathways (69).

Bcl-2 is an important endogenous inhibitor of programmed-cell death *in vitro* (70). It is induced after experimental TBI (71) and reduces cortical tissue loss (72). Bcl-2 is increased in injured brain after severe TBI in humans (54). CSF levels of bcl-2 were increased ~4-fold in TBI compared with control patients. Moreover, CSF bcl-2 was associated with patient survival (73).

Clearly there is now substantial evidence, even in the clinical setting, for an important role for delayed neuronal death by apoptosis or mixed “apo-necrotic” phenotypes after severe TBI. This may represent a valuable opportunity for the development of new therapeutic approaches in the future.

#### CELL SIGNALING ABNORMALITIES IN NEURONAL DEATH

Neuronal death occurs after both experimental and clinical TBI. In addition to regions of brain directly contused, the hippocampus appears particularly vulnerable to TBI (74–78). As previously discussed, cell death execution pathways are activated by a sufficient severity of TBI involving mitochondrial injury, cytochrome C release with caspase activation, AIF release, and receptor-coupled pro-death pathways. Neurotransmitters, neurotrophins, cytokines, other growth factors, and oxidative stress activate multiple upstream signaling pathways linked to either pro-survival or pro-death activities (79). These receptors couple to signal transduction pathways involving interactions and cross-talk between multiple serine/threonine and tyrosine protein kinase cascades.

Many kinases involved in cell death process are serine/threonine protein kinases. Important participants in the cell death cascades include the mitogen activated protein kinases (MAPK). MAPKs cascades are complex and are mediated by successive protein kinases that sequentially activate each other by phosphorylation. They are importantly linked to two key components of

the cell death cascade, jun kinase (JNK) and P38 MAPK (Figure 8-5). JNK and p38 MAPK pathways activate caspase-3 (80–82). Activation of JNK leads to induction of pro-death genes including FasL (81–83). JNK increases p53 and Bax levels which increase cell death. JNK and p38 function in different stress signaling pathways and both target similar nuclear transcription factors that can be activated by pro death stimuli such as oxidative stress (84). Studies in various TBI models have documented significant changes in both JNK, and p38 MAPKs that may be related to cell death and functional impairment after injury (85–87). MAPKs are also linked to survival signals through the ERK pathway, highlighting the complex cross-talk between these cascades (Figure 8-5).

Several protein kinase cascades play a major survival role. Phosphoinositide 3-kinase (PI3-K), protein kinase B (PKB), and protein kinase A (PKA) pathways are prototype examples (Figure 8-6). PKB is also called akt; the complex nomenclature of these kinases has evolved across many disease processes. PKB is activated upstream by PI3K in response to survival signals, and have numerous pro-survival, growth, differentiation and synaptic plasticity actions (88, 89). PKB affects survival by a number of mechanisms including the phosphorylation and inactivation of several pro-death mediators such as Bad. Bad, a member of the Bcl-2 family, is phosphorylated by PKB at ser136 resulting in Bad dissociation from Bcl-xL and binding to 14-3-3 proteins inhibiting cell death

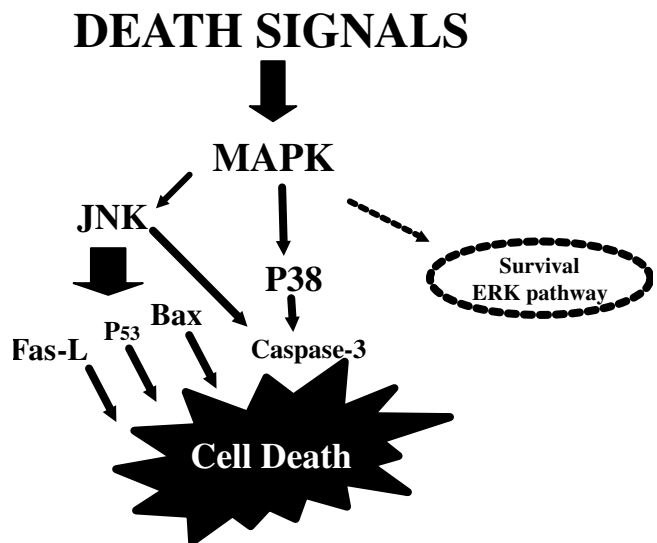


FIGURE 8-5

Cartoon showing the role of mitogen-activated protein kinases (MAPK) in transducing the signals involved in neuronal death. For example, oxidative stress triggers MAPK activation with resultant activation of jun kinase (JNK) which facilitates neuronal death mediated by a number of mechanisms including death receptors (Fas-Fas-L), P53 and Bax. MAPK also involves cross talk with some survival pathways such as ERK



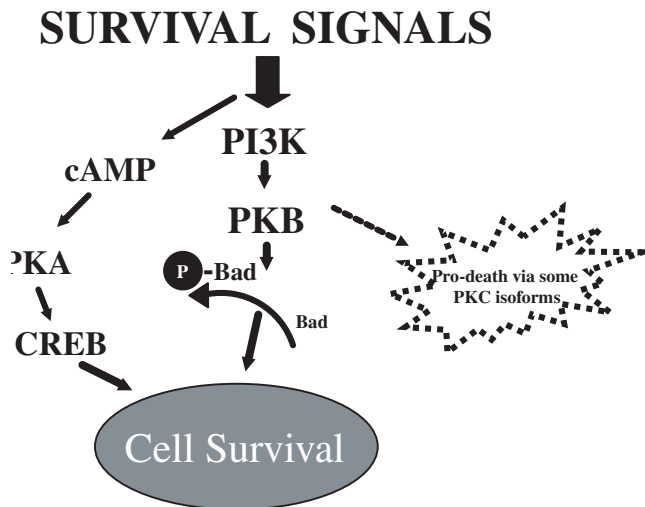


FIGURE 8-6

Cartoon showing the role of important survival signal-mediated kinase activation in promoting neuronal survival. Phosphoinositide 3-kinase (PI3-K), protein kinase B (PKB), and protein kinase A (PKA) pathways are involved. PKB affects survival by a number of mechanisms including the phosphorylation and inactivation of the pro-death mediator Bad. Phosphorylation of Bad results in its dissociation from Bcl-xL inhibiting cell death. CAMP-mediated activation of PKA can also lead to formation of the transcription factor “cAMP response element binding protein” (CREB), which also promotes cell survival

(Figure 8-6) (90). CAMP-mediated activation of PKA can also lead to formation of the transcription factor “cAMP response element binding protein” (CREB), which is similarly associated with cell survival. These pro-survival kinase pathways are outlined in Figure 6 (83). Survival signals are exemplified by growth factors, cytokines, hormones, cell-cell interactions as well as extracellular matrix adhesion molecules. Of course, inactivation of two pro-death members of the MAPK family, p38 and JNK/SAPK, have also been proposed as promoting survival by extracellular stimuli (91). Finally, activation of some PKC isoforms by PI3K can transduce pro-death signals, once again highlighting the complexity of these kinase cascades (Figure 8-6).

In summary, the complex but important kinase pathways are critically involved in the control of neuronal death and plasticity. Further insight into these cascades will likely lead to the development of powerful new tools to manipulate both neuronal death and rewiring after injury. Proteomics approaches may be essential to unraveling the cybernetic nature of these kinase pathways (92).

## AXONAL INJURY

Traumatic axonal injury (TAI) encompasses the spectrum of mild to severe TBI, both clinically (93–96) and in

models (97–99). The extent and distribution of TAI depend on injury severity and category (focal versus diffuse) (100).

The classical view that TAI occurs due to immediate physical shearing is represented primarily in severe injury where frank axonal tears occur (93,94,101,102). However, recent experimental studies suggest that TAI predominantly occurs by a delayed process termed “secondary axotomy” (98,103,104). Two hypothetical sequences have attempted to explain secondary axotomy, one attributing axolemmal permeability and calcium influx as the initiating event (Figure 8-7), the other a direct cytoskeletal abnormality impairing axoplasmic flow (98,104,105). It has been posited that both forms of reactive axonal swelling take place but in different proportions depending on the severity of injury. Superimposed on these theories is the finding that hypoxic/ischemic insults can also produce axonal swelling that resembles retraction balls. As a result, differing as well as unifying theories for axonal injuries in brain injury have been proposed (98,104–107). Common mechanistic features include focal ion flux, calcium dysregulation, and mitochondrial and cytoskeletal dysfunction.

TAI contributes to the morbidity after TBI (98, 100–102). Until recently the contributions of TAI to morbidity, have remained speculative since TAI has remained refractory to treatment even in the laboratory. However, recent studies in experimental TBI models have shown that hypothermia or cyclosporin A can both reduce TAI (108,109). In contradistinction, hypothermia reduces growth factor signaling after experimental TBI (110,111) that could blunt regeneration. These therapeutic advances should help determine more definitively the contributions of TAI to secondary damage. Recent application of MRI to the study of TAI (112,113) and axonal connectivity (114,115) may improve our understanding of TAI and regeneration.

## CEREBRAL SWELLING

In addition to cascades of neuronal death and axonal damage, brain swelling is a hallmark finding in severe TBI and results in the development of intracranial hypertension, which can have devastating consequences. Cerebral swelling and accompanying intracranial hypertension contributes to secondary damage in two ways. Intracranial hypertension can compromise cerebral perfusion leading to secondary ischemia. In addition, it can produce the devastating consequences of deformation through herniation syndromes. Intracranial hypertension results from increases in intracranial volume from a variety of sources, which are outlined in Figure 8-1. In some cases, such as with epidural, subdural or parenchymal hematoma formation, an extra-axial or parenchymal blood collection is the key culprit—and is generally

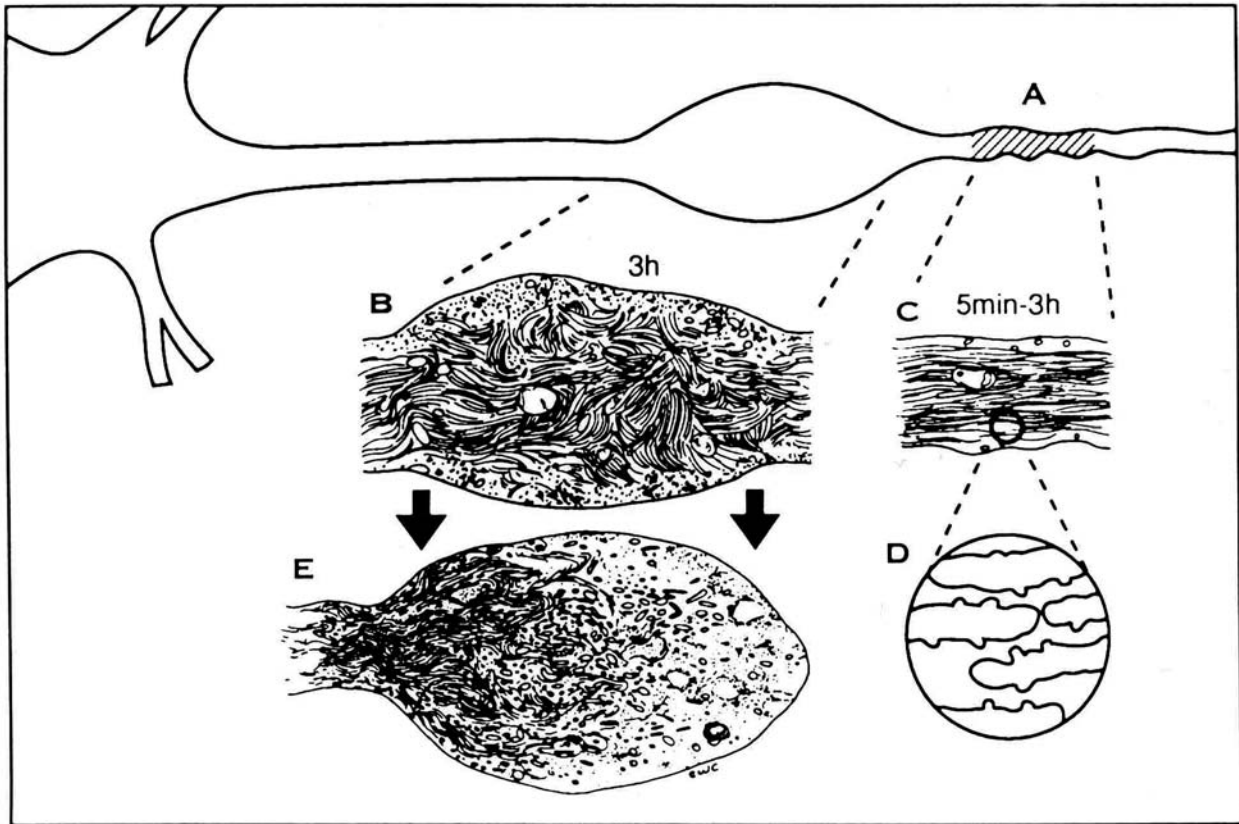


FIGURE 8-7

Reactive axonal swellings have been proposed to result from focal axolemmal disruption, ionic shifts and neurofilamentous compaction at site (A) results in a reactive swelling at site (B) in an upstream region of the axon. At the site of ionic influx, neurofilamentous compaction and mitochondrial swelling is seen (C). Neurofilament compaction is associated with neurofilament sidearm loss (D). Obstructed axonal transport results in upstream axonal enlargement, neurofilament misalignment, organelle accumulation, and formation of the typical reactive axonal swelling (E)

addressed by surgical evacuation (116). However, there are several important mechanisms that are more uniformly involved in the development of intracranial hypertension. These are related to either brain swelling from vasogenic edema, astrocyte swelling, and an increase in tissue osmolar load, or vascular dysregulation with swelling secondary to an increase in cerebral blood volume (CBV).

Recent data suggest that brain swelling after severe TBI results from edema rather than increased CBV. Marmarou et al. (117) measured both CBV and brain water in adults with TBI. Using a dye indicator technique (coupled to CT) to measure CBV and magnetic resonance imaging [MRI] to quantify brain water, increases in brain water were commonly observed, but were generally associated with reduced (not increased) CBV (Figure 8-8).

Thus, edema rather than increased CBV appears to be the predominant contributor to cerebral swelling after TBI. Both cytotoxic and vasogenic edema may play important roles in cerebral swelling. However, our traditional concept of cytotoxic and vasogenic edema is evolving.

There appear to be four putative mechanisms for edema formation in the injured brain. First, vasogenic edema may form in the extracellular space as a result of blood-brain barrier (BBB) disruption. Second, cellular swelling can be produced in two ways. Astrocyte swelling can occur as part of the homeostatic uptake of substances such as glutamate. Glutamate uptake is coupled to glucose utilization via a sodium/potassium ATPase, with sodium and water accumulation in astrocytes. Swelling of both neurons and other cells in the neuropil can also result from ischemia- or trauma-induced ionic pump failure. Finally, osmolar swelling may also contribute to edema formation in the extracellular space, particularly in contusions. Osmolar swelling, however, is actually dependent on an intact BBB or an alternative solute barrier.

Cellular swelling may be of greatest importance. Using a model of diffuse TBI in rats, Barzo et al. (118) applied diffusion-weighted MRI to localize the increase in brain water. A decrease in the apparent diffuse coefficient after injury suggested predominantly cellular swelling, rather than vasogenic edema, in the development

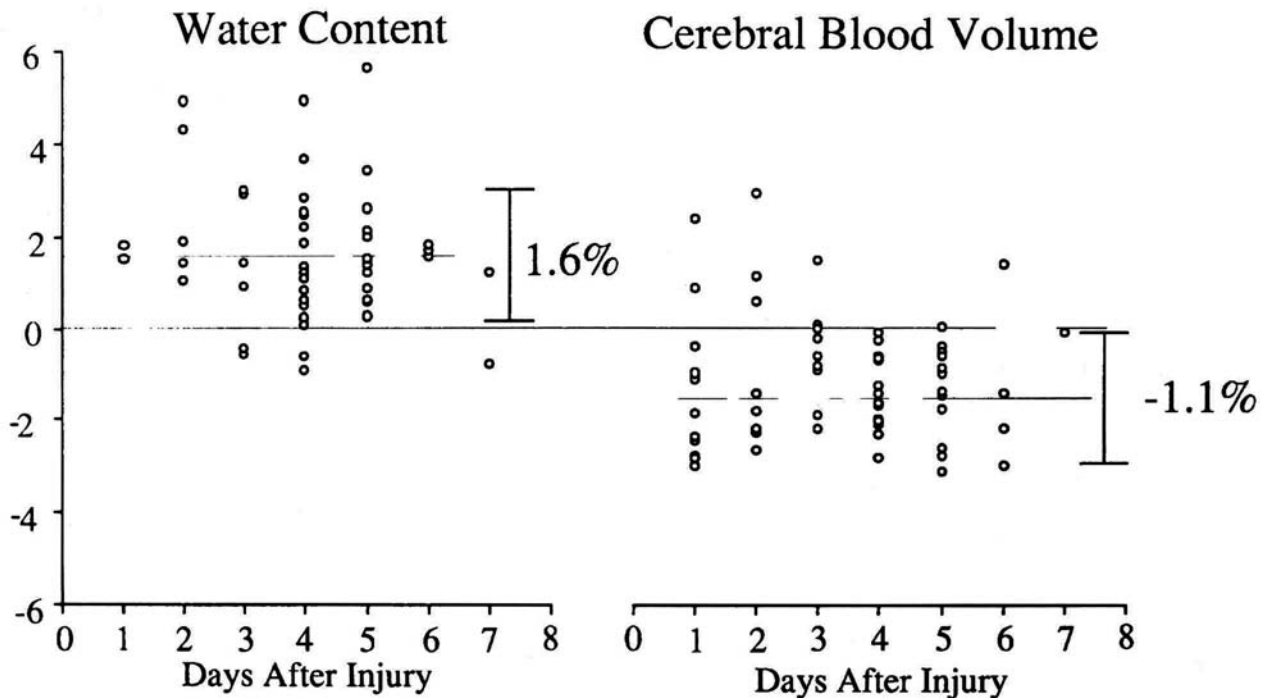


FIGURE 8-8

The percentage change in brain water content as assessed by MRI and cerebral blood volume (CBV) as measured by CT and indicator dilution technique in 109 studies of adults with TBI. Brain water is increased and CBV is reduced in adults with severe TBI. Reprinted from the work of Marmarou et al. (121) with permission

of intracranial hypertension. Cellular swelling may be of even greater importance in the setting of TBI with a secondary hypoxic-ischemic insult (119).

Katayama et al. (120) also suggested that the role of BBB in the development of post-traumatic edema may have been overstated—even in the setting of cerebral contusion. One intriguing possibility is that as macromolecules are degraded within injured brain regions, the osmolar load in the contused tissue increases. As the BBB reconstitutes (or as other osmolar barriers are formed), a considerable osmolar driving force for the local accumulation of water develops, resulting in the marked swelling so often seen in and around cerebral contusions (Figure 8-9).

In some cases, increases in CBV can be seen after TBI and contribute to intracranial hypertension. When an increase in CBV is seen, it may result from local increases in cerebral glycolysis “hyperglycolysis” as described by Bergsneider et al. (22). In regions with increases in glutamate levels, such as in contusions, increases in glycolysis are observed because astrocyte uptake of glutamate is coupled to glycolysis rather than oxidative metabolism. Recall that oxidative metabolism is generally depressed by ~50 percent in comatose victims of severe TBI in the ICU (20). Hyperglycolysis results in a marked local increase in cerebral glucose utilization with a coupled increase in CBF and CBV and resultant local brain swelling. A detailed discussion of this topic is beyond the scope of this chapter.

As MRI and MR-spectroscopic methods continue to develop and become applied to critically ill patients (121) our “black box” knowledge of the mechanisms involved in cerebral swelling should greatly advance. It must be remembered that although neuronal and axonal injury are key downstream events in the evolution of damage after severe TBI, brain swelling and resultant intracranial hypertension is still the principal target for titration of therapy in the ICU.

## INFLAMMATION AND REGENERATION

There appear to be both acute detrimental and sub-acute/chronic beneficial aspects of inflammation. There is robust acute inflammation after TBI. This has been shown in models of TBI (122–124), and in adult patients (125–128). NF- $\kappa$ B (129), TNF $\alpha$  (130, 131), IL-1 $\beta$  (132, 133), eicosanoids (134), neutrophils (123,135), and macrophages (136,137) contribute to both secondary damage and repair.

Markers of inflammation after TBI have been assessed in humans using two general strategies, (i) examination of inflammation in contused brain tissue resected from patients with refractory intracranial hypertension, and (ii) study of mediator levels in CSF. Consistent with a role for IL-1 $\beta$  in the evolution of tissue damage in

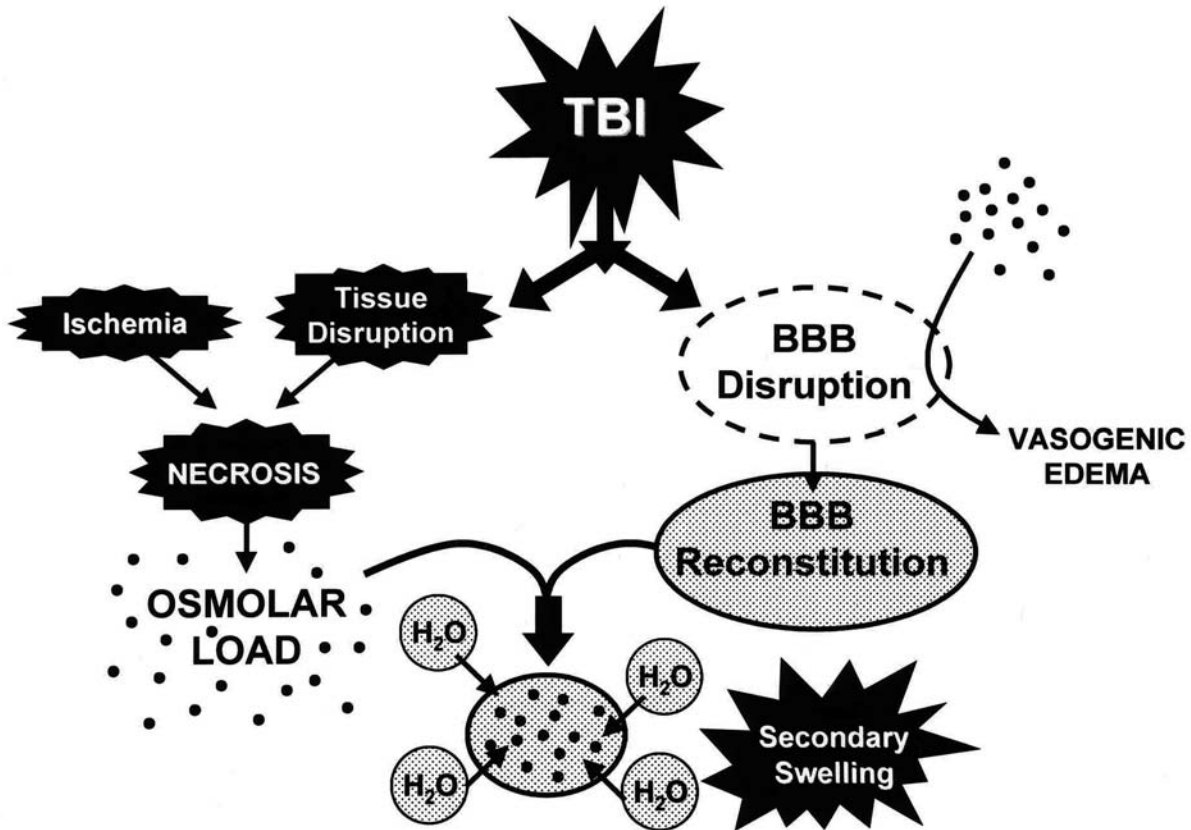


FIGURE 8-9

Schematic based on hypothesis of Katayama et al. (120) suggesting that as the osmolar load increases (breakdown of macromolecules in the region of contusion necrosis), a considerable driving force develops for the accumulation of water, resulting in the secondary swelling so often seen in and around cerebral contusions

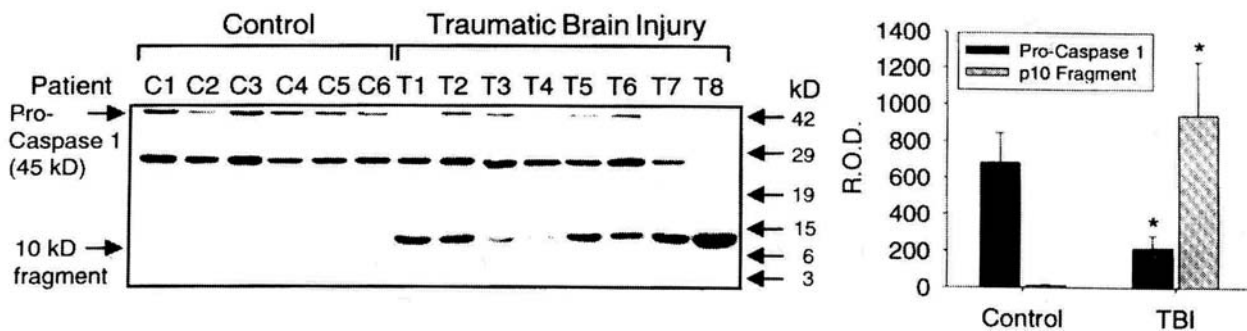


FIGURE 8-10

Evidence for activation of IL-1 $\beta$  converting enzyme (ICE) activation in cerebral contusions resected from adult patients with severe TBI and refractory intracranial hypertension. Western analysis demonstrating cleavage of the intact 45 kD pro-caspase-1 to the 10 kD fragment in each of eight victims of severe TBI but in none of 6 control brain samples from patients that died of non-CNS causes. Reprinted from Clark et al. (63) with permission

human TBI, Clark et al. (54) performed western analysis of brain samples resected from adults with refractory intracranial hypertension secondary to severe contusion. Interleukin-1-converting enzyme (ICE) was activated, as evidenced by specific cleavage in patients with TBI. ICE activation is critical to the production of IL-1 $\beta$ . ICE acti-

vation was not detected in patients that died of non-CNS etiologies (Figure 8-10). This supports the production of IL-1 $\beta$ , a pivotal pro-inflammatory mediator, in the traumatically injured brain in humans.

Studies of CSF further support a role for inflammation in TBI. Marion et al. (126) demonstrated increases

in IL-1 $\beta$  in CSF after severe TBI in adults. These increases were attenuated by the use of moderate therapeutic hypothermia. Similarly, there are increases of a number of cytokines in CSF after severe TBI including IL-6, and IL-8 (128,138). Contusion and local tissue necrosis appear to be important to trigger neutrophil influx with resultant secondary tissue damage (123). Neutrophil influx is accompanied by increases in inducible nitric oxide synthase (iNOS) levels in brain (124) and is followed by macrophage infiltration, which peaks between 24–72 hours after injury (139). Macrophage infiltration and the differentiation of endogenous microglia into resident macrophages may signal the link between inflammation and regeneration, with elaboration of a number of trophic factors (i.e., nerve growth factor (NGF), nitrosothiols, vascular endothelial growth factor) (133, 138,140,141).

Kossmann et al (138) reported a link between IL-6 production and the production of neurotrophins, such as NGF. Cultured astrocytes treated with either IL-6, IL-8 or CSF from brain-injured adults, produced NGF. Cytokine production after TBI may be important to neuronal plasticity and repair, as discussed below.

Studies in models of TBI (131, 142) suggest beneficial aspects of inflammation on long-term outcome. Mice deficient in TNF $\alpha$  exhibit improved functional outcome (versus wild-type) early after TBI. However, the long-term consequences of TNF $\alpha$  deficiency on outcome are detrimental (131). Similarly, despite a detrimental role for iNOS in the initial 72 h posttrauma (143), iNOS deficient mice demonstrated impaired long-term outcome vs controls (142). iNOS is important in wound healing and iNOS-derived nitrosylation of proteins may play a role (141,144). Regeneration and plasticity play important roles in mediating beneficial long-term effects on recovery, and these responses are linked to inflammation.

The contribution of the inflammatory response to TBI remains to be determined. Although there are a few promising reports in models of the use of anti-inflammatory therapies in TBI and ischemia (targeting IL-1 $\beta$ , ICE, and TNF $\alpha$ ) it is unclear whether anti-inflammatory therapies will improve outcome after clinical TBI. If inhibition of the inflammatory response is considered, exacerbation of infection risk must also be anticipated (145). Also, the link between inflammation and regeneration must be recognized.

## CONCLUSIONS

Mechanisms involved in the evolution of secondary brain injury after TBI have been reviewed. Particular attention has been paid to studies at the bedside. Our understanding of the biochemical, cellular, and molecular responses has progressed—particularly with the application of

molecular biology methods to human materials. Additional details on these mechanisms have also been reviewed in a companion article to this chapter which addresses the unique setting of pediatric TBI (146). Future investigation should integrate these findings with bedside physiology and an improved assessment of outcome. Finally, novel imaging and diagnostic methods, particularly MRI and MRS must be coupled with biochemical and molecular methods to clarify the mechanisms involved in secondary damage and the local effects of novel therapies.

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# 9

## Concepts of CNS Plasticity and Their Implications for Understanding Recovery After Brain Damage\*

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### CONCEPTUAL AND THEORETICAL ISSUES IN RECOVERY OF FUNCTION: BACKGROUND

It is often taken for granted that after brain injury, “plasticity” and recovery may be possible, but their underlying mechanisms remain a matter of debate. The term “plasticity” is seldom explicitly defined in reports on neurorehabilitation. When any functional restitution or recovery after brain injury is observed, the assumption is that the inherent plasticity of the brain is responsible for the beneficial outcome. But what does this really explain about what is actually taking place in response to brain damage?

Until the 1960s, very few people in the field of neurorehabilitation supported the idea that the adult central nervous system (CNS) was capable of undergoing any substantial reorganization in response to brain damage, so any “recovery” was attributed to strategic behavioral tricks that brain-injured subjects were able to master in order to overcome their deficits (1). These were referred to as “compensatory strategies,” but the argument was circular: you had behavioral recovery because of compensatory strategies which were inferred because you had behavioral recovery—hardly a meaningful explanation of mechanism!

One of the main dogmas that blocked substantive research and clinical understanding of the mechanisms of recovery in response to brain damage was promoted by the Nobel prize-winning neuroanatomist Ramon y Cajal (2), who forcefully argued that once development was over, any regeneration in the adult brain would be very limited, if it occurred at all. During that era, neuroanatomists who observed structural changes in the damaged adult brain—now considered characteristic of neuronal repair, such as axonal or dendritic sprouting, or even neurogenesis—often reported such changes as mere artifacts of histological techniques rather than as real evidence of CNS structural plasticity.

The paradigm shift that led to acceptance of the idea of CNS plasticity in response to injury began with the work of Raisman (3). Using then state-of-the-art electron microscopic techniques, Raisman first mapped the two primary afferent pathways into the subcortical structure he called the “septal nuclear complex” in adult rats. Once the pathways were identified, Raisman made separate and selective knife-cuts to disrupt one of the two paths to observe what changes would take place in the intact pathway in response to the injury. After waiting a suitable period of time he observed that (1) degenerating fibers

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caused by the cut left synapses in the septal nucleus vacated, and (2) fibers from the surviving pathway reoccupied the vacated synapses. Particularly interesting was that the new afferents were “heterotypic”: they did not provide the same neurotransmitter to the septal cells as had the original fibers. Raisman concluded that:

the finding that the distribution of one fibre pathway to the septum is altered by the destruction of another system of septal afferents suggests that synapses in the central nervous system of adult mammals may be far more labile than had been previously suspected. It is interesting to speculate why, in view of this anatomical plasticity, so little functional recovery accompanies lesions of the brain (p. 45).

Raisman and his colleagues did not follow up his remarkable observations with behavioral studies, but his work did lead others to change the view of the adult CNS from a static, phrenological collection of structures with fixed functions to a much more dynamic system capable of reorganization in response to injury (see, e.g., Cotman [4] and Steward [5]).

Although studies on promoting recovery of function appeared as early as the first few decades of the twentieth century (see Finger and Stein [6] for examples), until the early 1970s they were largely dismissed by the field as describing “anomalous” events not worthy of serious study. At the behavioral level, those adhering to the static view of the adult CNS could claim that when functional recovery was observed, it was simply because the tests being used were not sensitive enough to detect the underlying deficits.

The idea that recovery of function can be promoted by pharmacological agents, the transplantation of fetal or stem cell tissues, environmental stimulation, hormonal factors, and other means, is a very new concept in the history of the science and is still not completely accepted. For example, the indisputably best-selling textbook in neuroscience, used today in almost all comprehensive graduate neuroscience classes, is *Principles of Neural Science* (7). This work refers to plasticity only once (p. 34), and despite its comprehensive coverage and its heavy use by medical and biomedical professionals, it offers no discussion of recovery of function and its implications for thinking about the organization and adaptability of the brain in response to injury.

Grounds for cautious optimism may exist, however. In a new textbook closely modeled after Kandel et al., *Fundamental Neuroscience* (8), the authors do refer to “experience-driven plasticity” in the cortex and other neural systems, but they say nothing about any aspect of recovery of function and its potential underlying mechanisms. This blind spot in the basic education of young neuroscientists can have profound effects on the treatment of CNS injury and the allocation of resources for

research. Certainly no one is claiming that physiological repair of the damaged brain or spinal cord is going to occur under *all* conditions, but it is becoming impossible to ignore or deny the many hundreds of laboratory animal and human studies which have shown that some extent of repair, regeneration and functional recovery can be stimulated under some conditions. The focus should now be on determining what those conditions are, and applying them to achieve repair after degenerative or traumatic injuries to the brain or spinal cord.

The remainder of this chapter reviews several concepts of recovery that were proposed in the fields of neuropsychology and neurorehabilitation before there was much empirical and clinical data to support them. Given the large body of evidence we now have for dramatic reorganization and repair after injury, are these early concepts of functional recovery consistent with the well-accepted ‘principle’ of strict functional localization in the brain? Are plasticity concepts and localization dogma consistent with each other? Is localization dogma supported by the evidence, both modern high-tech data and the older intuitive clinical approach (9)?

First, is it clear what we mean when we use the term “neuroplasticity”? Is it a specific, well-defined phenomenon that can be applied as an explanatory construct? Over the last decade or so, there has been an explosion of interest in neuroplasticity and it is often taken for granted that what the term implies is well understood and accepted. PubMed, the National Institutes of Health’s literature search engine, is a powerful tool for finding the most current articles in the biomedical sciences. Type in the word “neuroplasticity” and about *eleven thousand* articles appear. Neuroplasticity is applied to the symptoms of Alzheimer’s disease, alterations in apolipoprotein E synthesis, chronic pain, mood disorders, recovery from stroke, long-term potentiation in the hippocampus, changes in memory in development and aging, allodynia, presynaptic neurotransmitter vesicle release, changes in synaptic terminal arborization, alterations during critical periods of development, alterations in glutamate receptors, changes in trans-cranial stimulation-induced excitability of the motor cortex, alterations in sensory-cortical maps, neurogenesis during development and aging, stem cell effects, axonal sprouting, epileptic seizure activity, and augmentation of immune-induced neural inflammatory response, all in the first twenty references that come up in PubMed! How can such ubiquitous use of the term be of any use in understanding what is actually occurring in the damaged nervous system in response to injury? One argument is that, clearly, ‘plasticity’ has manifold ways of expressing itself in both the intact and the damaged nervous system. But if every type of change in neural tissue is seen as plasticity, what then is NOT an example of the phenomenon?

Here is a case, taken from the field of neurogenesis, that illustrates the problem: recently, Parent and

Lowenstein (10) reviewed the literature on the effectiveness of stem cell proliferation in the adult nervous system of rodents. These authors reported that there is, indeed, a five- to tenfold increase in the number of dentate granule cells in the hippocampus following chemotoxic injury to the brain, and this could certainly be considered a dramatic example of injury-induced neuroplasticity. However, their review of the literature also showed that the neurogenesis was associated with increases in kindling and seizure activity in the hippocampus and with a later increase in apoptotic cell death. This is not to imply that, under all conditions, injury-induced neurogenesis would be detrimental. But this is a typical example of neuroplasticity that has a negative outcome. But if such a phenomenon (i.e., neurogenesis as a cause for post-traumatic epilepsy) is also an example of ‘plasticity,’ then just how useful is the concept for explaining recovery of function? Perhaps we need to distinguish between *negative* and *positive* plasticity and to think more critically about how we use the term to describe events in the central nervous system (CNS) associated with functional recovery and rehabilitation.

For the purposes of this review, “neuroplasticity” will be used only for verifiable examples of functional and adaptive recovery after brain injury. This is the behavioral concept that cognitive, sensory, or motor impairments gradually diminish or are eliminated over time rather than getting worse. Limiting the term in this way implies that there can be acute or chronic deficits which disappear spontaneously, or which can be reduced by pharmacological, physiological, surgical, or behavioral treatments over time (11–15).

### **“LOCALIZATION OF FUNCTION,” RECOVERY OF FUNCTION, AND DEFINITIONS OF NEUROPLASTICITY**

In the clinic, it may be difficult to accept a very limited definition of plasticity. This is because it is often necessary for brain-damaged patients to succeed in a variety of activities of daily living by substituting new behavioral strategies. This substitution is considered a form of ‘compensation’ or adaptation to a deficit. As noted earlier, some critics of the concept postulate that recovery of function does not really exist. They hold that all recovery is only a type of compensation (see [1] and [16] for a good discussion of this issue). This view is an offshoot of the idea that specific areas of the brain are genetically programmed to control or mediate behaviors, so the destruction or perturbation of a center in which such specific functions are localized leads to the permanent loss (or serious impairment) of that function.

The battle between those who argue for precise localization and those who think that functions are more widely

distributed throughout the brain has been going on for more than a hundred years, and despite breakthroughs in brain imaging techniques, no resolution is in sight. Within this framework the limits or extent of localization seem to shift with the latest fashions in technology. For example, cortical maps grow or shrink according to how imaging methods are applied, and this determines how the loci of control are defined. As imaging studies proliferate, structures are added or subtracted at will to the number required to mediate a particular function, with the expansion taking place in the serial or parallel circuits so popular in computer-based metaphors of the brain. The more recovery observed, especially in the case of bilateral structural removal, the more structures have to be added to account for the observed plasticity. This issue is discussed further below.

Providing technical support for this conceptual approach to brain function is the rapid progress in molecular biological assays, which has led to a plethora of functional activities being assigned to the expression or inhibition of specific genes, a form of localization doctrine gone wild—a molecular biology of phrenology, so to speak, which is of growing concern to some investigators in this field. In an excellent brief review of the issue, Kosik cautions that:

Genes, neurons and brain regions are annotated with functional descriptors that fail to capture the interactive nature of these units. The temptation is strong to jump beyond what a biological unit actually does, to a more encompassing functional label. For example, a mutant gene does not cause a disease; it merely encodes a mutant protein that leads to a cascade of events and, eventually, to a disease. The methodology to ascertain function can also be limiting. Just as the carpenter, whose only tool is a hammer, treats all objects like nails, so neurophysiologists and brain ‘imagers’ probe the brain with their own hammers and have cobbled a picture of brain function that is not explicitly integrated (17).

This discussion is not just an academic exercise, because one corollary of the ‘strong’ form of localization is that one can never expect to see any ‘true’ recovery of function, and perhaps it is because of this belief that recovery of function per se is rarely discussed in the major textbooks of basic neuroscience currently in use. These argue that subtle “tricks” must be used by the organism to perform effectively, and that the tricks may be too subtle to detect without sophisticated behavioral testing designed to reveal the underlying deficits and shifts in behavior (1). If no deficits are observed, it is because the tests are insensitive, or the wrong tests have been used, rather than because any true recovery of function has occurred. From this perspective, the job of the neuropsychological diagnostician is to tease out the deficits and prove the localization.

The only goal of rehabilitation, in this context, is to teach the patient new strategies to replace functions lost by the injury, and plasticity is defined by the extent to which such substitution is possible. For those who envision the nervous system as a kind of 'black box,' there is no need to speculate about underlying neural mechanisms or to worry about providing neuroprotection or enhancing neuroregeneration through a pharmacological or physiological substrate. The remaining brain tissue just does what it does to varying degrees of effectiveness, so why bother with trying to 'add' neurons or rebuild damaged circuits? Thus it is argued that while the brain-damaged patient may eventually accomplish the same goals as an intact individual, the means by which the task is accomplished may be very different.

### EQUIPOTENTIALITY, VICARIATION, CNS REORGANIZATION AND RECOVERY OF FUNCTION

The assumption of substitution rather than restitution of function after brain damage fits well with the idea that intact parts of the brain can take over the functions of tissue lost or destroyed after injury or disease. In this paradigm, remaining healthy tissue is said to modulate its physiological activities to compensate for the damage to a specific area. But there is evidence to support a different model for response to injury. Thus, in laboratory rats and monkeys, if injury occurs during certain critical periods in early development, recovery of cognitive and motor functions can sometimes be greater than that seen in adults with similar kinds of CNS damage. Is this merely a form of compensatory strategy or is structural reorganization of the brain itself a major factor in the resulting plasticity?

In humans with early brain injury, the issues are more complex and controversial than for adult brain injury, especially with respect to intellectual skills, language and cognition. For example, there are many studies in both animals and children that provide strong substantiation that early brain damage is associated with long-term deficits and intellectual impairments in later life (18, 19). Other studies support what has been called the Kennard principle (20), that early brain lesions lead to much more sparing than the same injury in a more mature organism (21, 22).

How is it possible to reconcile these divergent findings? It now appears that there are a number of factors that can predispose to better recovery if injury occurs during early development, but there are also factors that can make matters worse. One of the most important of these factors appears to be a very specific, critical period for plasticity such that very early-occurring injury to the brain may be much worse than if the injury were to occur just

a few weeks or months later (23). Bryan Kolb and his colleagues have repeatedly demonstrated this phenomenon in laboratory rats. They also review evidence in human infants showing that if a cortical injury occurs within the first months of life, the results can be devastating, but if the same cortical area is damaged at around one to two years of age, there is much better recovery. Kolb and Cioe (24) found that even as little as one week of difference in age could have dramatic impact on morphogenesis and sparing of function after medial frontal cortical lesions in rats. Thus, if the lesions were done on post-natal day 2, animals tested as adults on spatial learning and reaching tasks were very impaired. If the same surgery was done on post-natal day 9, there was extensive recovery and apparently substantial generation of new neurons to replace those that were removed by the surgery. In development, then, the precise timing of the injury *may be critical* in determining whether or not recovery will be observed, and when or whether rebuilding of neuronal circuits may occur. Injuries occurring slightly or moderately later than immediately after birth, when one might assume the most plasticity, could lead to much better outcomes. This calls for a more modulated evaluation and interpretation of the Kennard Principle that the earlier the injury the better the outcome.

When such sparing of function is observed during development or at maturity, it is often attributed to the equipotentiality or vicarious function of cerebral (usually cortical) areas. Equipotentiality refers to the capacity of anatomically distinct areas of the brain to mediate a rather wide variety of functions. Despite the caveats discussed above, such plasticity is thought to be more likely when the brain is developing and not yet specialized for particular activities such as speech or patterned movement, but there is both historical and contemporary evidence to suggest that both equipotentiality and vicarious function can be induced in the adult organism as well.

The concept of neural vicariation implies that even the mature CNS has a certain number of redundant or backup subsystems that participate in this takeover of function (25). However, the mechanisms by which area *a* could "take over the function" of damaged area *b* and still perform function *a* are usually not described. If there is substitution or vicarious function, how can it be determined at the physiological and/or behavioral levels of analysis? In one study in adult squirrel and owl monkeys, Xerri, Merzenich, Peterson and Jenkins (26) trained the animals to retrieve small objects, used microelectrode techniques to map responsivity to afferent activity when the animals performed the tactile discrimination tasks, and then selectively damaged specific parts of the sensorimotor cortex by electrocoagulation of surface blood vessels. The brain tissue was then checked to make sure that it was completely unresponsive to any peripheral stimulation.

Immediately after the lesions the monkeys were retrained on the tasks and cortical remapping was performed. The resulting changes in post-injury behaviors were complex and highly individualistic, suggesting from the outset that early experience and perhaps genetic factors played a role in the extent of cortical reorganization and recovery of digit and hand use. Performance initially deteriorated, then started to get better with re-training, and appeared to be proportional to the difficulty of the task. In some cases, animals with large lesions actually recovered better than those with less damage. The two different strains of monkeys did not perform the same way, indicating that initial brain organization and reorganization may be different across strains.

Most dramatic was the fact that the post-lesion reorganization of the cortex was very variable across monkeys; completely new cortical fields representing the fingers emerged and were enlarged in cortical areas that are not normally responsive to cutaneous stimulation. The changes appeared to be due both to the lesion and to the training procedures. According to the authors, the representation of the hands in the SI region of the somatosensory cortex is topographically organized into discrete cytoarchitectonic and functional regions, so that when these regions are damaged, area-specific deficits can be observed. For example, damage to area 1 leads to deficits in the discrimination of textures, while damage to area 2 impairs recognition of size and shape. Damage to area 3 causes significant deficits in texture, size and shape discriminations. These observations suggest that areas not normally involved in mediating certain types of behaviors can 'take over' those functions under the right circumstances—an example of vicarious function as we have used it here. This means that when behavioral substitution occurs, there are specific physiological mechanisms to subserve the changes. More important, we also think it means that the brain is not just functioning as it did before but without a part. Rather, there is extensive permissive reorganization of neuronal activity (and structure) underlying vicarious function. These findings also highlight the importance of applying the appropriate rehabilitation strategies at the appropriate time to enhance adaptive cortical reorganization (27, 28).

Yet such reorganization may demand a high price: the emerging patterns could prevent true restitution of function by encumbering the brain with an experience-induced reorganization that would be difficult or impossible to undo. Until the recent development of sophisticated imaging and electrophysiological techniques, it was not possible to determine whether such equipotential, vicarious, or pluripotent systems did or did not exist. Recent studies using functional magnetic resonance imaging (fMRI) and other related techniques such as positron emission tomography (PET) scanning show that functional compensation may be due to extensive reorganization of activity in the damaged brain.

For instance, after an infarct in the striatum of human patients, a number of subcortical areas both ipsilateral and contralateral to the injury site become activated as behavioral recovery progresses. The activation, measured by increases in cerebral blood flow (CBF) and glucose metabolism, is not observed when normal, healthy volunteers are asked to perform the same motor tasks. Thus, if 'tricks' are being employed to compensate for lost functions, they could be mediated by shifts in the activity of cerebral structures that are not initially involved in the behaviors (or at least not in the same way) under normal circumstances. This type of reorganization can take weeks, months, or years to occur (29).

In an earlier report typical of studies on compensation, Castro-Alamancos, Garcia Segura and Borrell (30) showed that after bilateral injury of the sensory-motor cortex in rats there is a substantial deficit in bar-pressing response to prevent aversive stimulation. If the injury is followed by direct-brain stimulation of the ventral tegmental nucleus, substantial recovery of the bar-press behavior is observed. Under these conditions if the hindlimb sensory cortex in the recovered animals is ablated, the deficit returns. It is important to note that the ablation of this area in the first place does not cause the same deficit, and this is taken as evidence of compensatory shifts in cortical function; the hindlimb area "assumes the role of another area after induced recovery from brain damage".

In another example of shifts in function thought to be compensatory, Buckner et al. (31) used PET and fMRI scanning techniques to examine the preservation of speech using a variety of linguistic and cognitive tests in a 72-year-old patient one month after a stroke in the left-inferior frontal cortex. Although the patient was impaired in speech generation tasks, he was able to access words when given partial words as cues, a task that usually depends (according to the authors) on an intact left-inferior frontal cortex. The scanning during performance showed that the right-inferior prefrontal area was activated during the tasks. "This area is not typically activated by normal subjects performing word-stem completion and appears to be used (by the patient) to compensate for his damaged cortex" (p. 1253).

One of the most interesting forms of 'spontaneous' recovery in both animals and humans is seen in the 'serial lesion' effect (see [6] for a more detailed review). In this type of injury, lesions are inflicted in stages so that, for example, the left frontal cortex may be extirpated and then a second operation takes the homologous right frontal cortex thirty days later. Under these conditions, both animals and humans show remarkable and robust post-injury sparing of function compared to counterparts with the same damage inflicted in one stage [again, see (6)]. In humans, slow-growing injuries often do not lead to either the severity or sometimes even the appearance

of the functional impairments noted when the same extent of injury occurs after a stroke or acute traumatic damage (32). Although there are numerous replications of the serial lesion effect in fully mature subjects, the research has not been the focus of much attention in contemporary neuroscience. This is probably because the instances of plasticity as demonstrated by considerable sparing of function *in the absence of special training or treatment* is problematic for current theories of highly organized modular function (see 6, 33–36 for examples). Thus, in the face of bilateral removal of a structure with no loss of function, it is difficult to sustain the notion that individual aggregates of cells or structures are critical for the expression of that function. Fortunately, current literature is beginning to take another look at what such plasticity implies for concepts about the organization of function in the adult CNS.

A few years ago, Seitz and Freund (37) reviewed human studies showing that slowly progressive lesions often remain asymptomatic for years because the space-occupying tumors cause a substantial reorganization of function as measured by regional CBF (rCBF) studies. These investigators studied a group of patients with brain tumors which invaded all of the hand/arm motor cortex, and who had developed seizures but were normal on neurologic examination. The rCBF showed that during finger movements the areas of activation were substantially displaced to more lateral positions, even to cortical areas outside the motor strip. The authors concluded that “the astonishing discrepancy between the functional consequences of acute versus chronic lesions of the nervous system raises the possibility that reorganization (of function) is not restricted to within-system recovery in the motor cortex” (p. 329). This type of slowly developing reorganization can be considered as evidence for equipotentiality or vicarious function in the broad sense. The authors also point out that over time, the patients learn to use and refine other behavioral strategies often seen in normal subjects. It is thought that such patients can be given substantial skill training to recruit other cortical areas into the functional reorganization produced by the demands on the damaged CNS.

Equipotentiality and vicarious function are perhaps most easily dramatized (and contested) in cases of brain injury during postnatal development. In the 1960's, the developmental psychologist Eric Lenneberg (38) proposed that, at birth, the two cerebral hemispheres are equipotential for cognitive and language functions, and only gradually become specialized as the child matures. This idea seemed to be supported by the now classic studies of Margaret Kennard in monkeys. She showed that animals with large cortical lesions inflicted early in life showed none of the extensive deficits seen when the same type of damage was inflicted at a later age (39). Subsequently, Patricia Goldman was able to show that early

brain lesions in monkeys led to substantially more sparing of cognitive functions than when the damage was inflicted in later life. Goldman and Galkin (40) reported that lesions of the frontal cortex in a fetal rhesus monkey operated on and returned to the womb until term not only showed complete sparing of cognitive function, but also demonstrated a radical reorganization of the entire cortical mantle evidenced by numerous ectopic gyri and sulci not seen in the intact animal.

It has become increasingly clear that the twin dogmas of specific localization and complete equipotentiality need to be re-evaluated in the face of better data and experimentation. In an excellent brief review of this literature, Vargha-Khadem et al. (41) reported that better testing of children has revealed residual deficits after early hemispheric removals. They note that some of these residual deficits could have been due to medications, seizures, and nutritional and other environmental factors. When such variables are controlled, the authors observe that, as equipotentiality theory would predict, the deficits are extremely mild considering the extent of tissue loss. According to Vargha-Khadem et al., either hemisphere does appear to be able to subserve linguistic and cognitive functions during the early stages of development; however, the cost of such ‘compensation’ may be a generally reduced level of such functions as visuospatial behaviors, caused by ‘crowding’ of the supposedly lateralized functions into the one remaining hemisphere (25).

#### DIASCHISIS, FUNCTIONAL INHIBITION, AND RECOVERY

More sophisticated imaging and electrophysiological techniques have been employed with increasing frequency to support the idea of diaschisis proposed by von Monakow at the beginning of the last century (42). In this early concept, brain injury triggers a form of long-lasting inhibition of neural activity that von Monakow called diaschisis. The inhibition is not limited to the site of injury but can spread to distal regions by means that were not clearly understood until fairly recently. Now we know that injury-induced biochemical and genomic alterations in protein synthesis can generate actions that are many synapses removed from the initial site of damage. The changes occur not only in the affected hemisphere, but also in the ‘intact’ contralateral homologues (see [51] below). Von Monakow postulated that recovery of function occurred as diaschisis dissipated over time, while permanent deficits were the result of permanent diaschisis.

Although the logic may appear circular, current research shows that injury to the brain does produce chronic suppression of activity associated with behavioral impairments (43–46). Agonist drugs which increase neurotransmitter activity or block inhibitory neurotransmitters

have been used to promote functional recovery after stroke in both animal (47) and human (12) subjects. However, clinical trials with these agents have had apparently limited success (48). Can behavioral therapy (e.g., the forced-use paradigm) or treatment with stimulants (e.g., amphetamine) reduce or eliminate the diaschisis caused by the injury? Do other brain areas ‘take over the function’ of the area of stroke? Current evidence can be cautiously interpreted to suggest that this may be the case (14). It is often reported that a stroke (experimental or naturally induced) leads to functional reorganization in brain tissue immediately adjacent to the injured area, but there are also significant changes in the contralateral homologous regions. In one study, twelve patients with acute strokes had unilateral arm weakness and some ability to move the arm after one month. Six of the patients showed good recovery and six did not. The six with good recovery showed much more activation of the cerebellar hemisphere opposite the damaged corticospinal tract than did the poorly recovered patients (49). The authors suggested that the recovery could have been due to diaschisis, or unmasking, of the functions in the contralateral cerebellum.

In a recent review, Price and colleagues (50) introduce the concept of dynamic diaschisis. They suggest that the environmental context as well as the locus of damage can play a role in determining functional outcome (36). Price et al. propose that:

the basic idea behind dynamic diaschisis is that an otherwise viable cortical region expresses aberrant neuronal responses when those responses depend on interactions with a damaged region. This effect might arise because normal responses in any given region depend upon driving and modulatory inputs from, and reciprocal interactions with, many other regions. The regions involved will depend on the cognitive and sensorimotor operation engaged in at any particular time (p. 419).

In other words, areas of the brain that are distant from the area of injury, even including the contralateral hemisphere, can show abnormal responses when the functional demand on the damaged tissue increases.

The authors conclude that dynamic diaschisis can be measured only with whole-brain functional imaging because one has to take into consideration the functional integration of many different brain regions. More important, “pathophysiological expression depends on the functional brain state *at the time the measurements are made*” ([50] p. 426, my italics). This can be taken to mean that brain structures may move ‘in and out’ of a state of diaschisis, depending on the functional demands made on them at a given time in the patient’s experience. It is interesting to note that, well before there was sophisticated imaging, this same point was made by the neuropsychologist Alexander Luria in 1966 (51).

### NEURONAL REORGANIZATION, UNMASKING, SPARING, LATENT SYNAPSES, AND FUNCTIONAL PLASTICITY

Thanks to refinements in microelectrode recording techniques, it has now been amply demonstrated in primates that certain brain areas such as the sensory motor cortex are capable of very rapid electrophysiological reorganization in response to brain injury. Thus, within very short periods of time after lesions of the afferent pathways or even after cortical damage, tissue adjacent to the affected areas reorganizes or expands its receptive fields to capture and mediate at least some of the original physiological activities that were destroyed by the injury. There is no doubt that such rapid reorganization occurs in a number of sensory and motor areas, but as noted earlier it must be emphasized that not all the reorganization is necessarily adaptive or beneficial to the organism.

Among the first to demonstrate injury-induced plasticity in the adult nervous system were Patrick D. Wall and his colleagues in the United Kingdom (52). Wall and his group first mapped the body surface of the ventral posterior lateral nucleus of the thalamus (VPL). This was done by tactile stimulation on the surface of the arms and legs of various laboratory animals. In a normal animal, the arm takes up two-thirds of the medial VPL and the leg occupies the lateral third. When inputs to the leg area were removed by unilateral excision of the gracile nucleus, the arm area expanded to “occupy two-thirds of the area previously responding to stimulation of the leg.” This change was noted within three days of the lesion. While this is an example of reorganization and cellular plasticity in response to injury, it is hardly an adaptive response to have an area that previously subserved inputs from the leg area now responding primarily to stimulation of the arm. Using other forms of temporary “deafferentation” such as blockage of nerve conduction by ice, Wall’s group was able to produce instantaneous remapping of cells in the lateral nucleus gracilis (LNG). Thus, the cells in the leg, normally activated by stimulation of the paws, now responded only to stimulation of the abdomen. In this case the unmasking of latent pathways was almost instantaneous, but, again, hardly adaptive with respect to behavioral utility.

Such changes in reorganization may be very long-lasting and dependent on post-injury experience. A number of years after the Wall experiments, Pons et al. were able to show that up to eleven years after a dorsal rhizotomy in adult rhesus monkeys, the brain region responding to stimulation of the hand (area 3b) responded instead to tactile stimulation of the face (53). In human patients, similar reorganization can be seen in phantom limb phenomena in response to amputation. This too has been taken as an example of neural plasticity in the adult nervous system (54, 55). These investigators found that



tactile stimulation of the face often led to referred sensations somewhere out on the phantom limb. Thus “there was a topographically organized map of the hand on the lower face region and the referred sensations were modality specific,” e.g., heat, cold, vibration, rubbing, etc. were felt as these same sensations at specific points on the phantom limb. The authors noted that this modality-specific referral from the face to the limb could occur only within a few hours after amputation, implying that the reorganized ‘localization’ of sensations must have been due to unmasking of previously silent pathways rather than any kind of structural or morphological changes *per se*.

Some patients report that, after a time, the phantom limb feels as if it is paralyzed or frozen into an excruciatingly painful clench with the fingers digging deeply into the palm. The patients cannot “will” the fingers to open and relieve the pain. Ramachandran and his group developed an ingeniously simple technique to provide relief, and in doing so again demonstrated the rapid reorganization of function that can occur in the appropriate context. Investigators asked patients to put their ‘normal hand’ into a box with a mirror in the sagittal plane of the hand. This gave a mirror-image of the normal hand, so it looked to the patients as if they had two hands opposing one another in the mirror-box. Now the investigators asked the patients to slowly open and close the normal hand while looking at the image in the mirror so it would seem as if the phantom hand was now opening and closing. The patients were surprised to find that while doing this exercise they actually felt movements in the phantom hand, but, more important, a number of the patients reported that seeing the phantom hand paradoxically unclench (because it was the normal hand they were seeing) relieved the cramping pain. This observation indicates that the amputation-induced reorganization may be undone by training and experience, with a novel engram replacing the maladaptive one.

Phantom limb effects are dramatic examples of reorganizational plasticity in the adult brain, but similar mechanisms can be seen in the visual and auditory systems when injuries are inflicted during early development. Thus Rauschecker (56, 57) has shown that if the visual (occipital) cortex is deprived of its inputs from the optic nerves, that same cortex can then be stimulated by auditory input. In other words, the ‘visual’ cells are ‘taken over’ by the auditory and somatosensory nerve fibers and thus both the auditory and somatosensory cortex could be said to expand into the territory previously controlled and occupied by visual inputs. Likewise, if the auditory cortex is destroyed or the auditory nerve is cut, the auditory cortex will be captured by visual inputs that have expanded into the deafferented zone.

Rapid reorganization tends to be more robust during early development, and this may be one reason why

young subjects with brain damage recover better than older counterparts with the same injury. Rauschecker asks what the post-recovery perception of animals brain-damaged during early development is like. Do they ‘see’ sounds and touches as in purported synesthesias, or does the visual cortex ‘change’ its functions to become auditory and/or somatosensory? What are the implications for the concepts of localization of function in the CNS during development and later in life?

Investigators also have shown that reorganization and expansion of functional cortical maps can be made to occur simply by providing intensive training experience in normal animals. Further, it appears that specific kinds of sensory training may be beneficial as rehabilitation therapy in brain-damaged subjects because it directly enhances the extent of rapid reorganization and functional plasticity. Nudo and his colleagues have recently reported that injury-induced reorganization and recovery of function can occur in the adult organism (58). Such recovery often requires experience-induced modifications in synaptic and cellular systems throughout the remaining healthy brain tissue that may not necessarily be contiguous to, or immediately involved in, the affected area and its functions. In other words, functions are widely distributed and in a constant state of dynamic interaction and change, not fixed and static as they are often represented in neuroscience texts.

It is clearly time to accept the idea that dynamic reorganization of functions is an ongoing event, not just a characteristic of the damaged brain, but a process that occurs in the course of normal activity and learning. Indeed, these changes may well serve as the basis for recovery mechanisms when there is an attack on the brain. For example, in accomplished musicians and athletes, somatosensory fields are markedly expanded compared to nontrained individuals. According to Nudo et al., highly repetitive practice on a tactile task in humans leads to marked expansion of the receptive field in the motor cortex which can persist for several months after the training is terminated. Maps also expand during the initial phases of training when the procedures are unfamiliar, and then shrink once explicit knowledge of the task has become habitual. (Nudo and his colleagues provide an excellent review of the various theories to account for this plasticity and the reader is urged to consult this paper.)

There are also apparently dramatic individual differences in the location and size of cortical receptive fields in normal individuals, which, in turn, vary in their degree of modifiability according to the subject’s experiential history (59, 60). At the very least, the notion that neuronal pathways can be rewired by the use of drugs or stimulation needs to be approached carefully, because the wiring diagrams for each individual may be heavily influenced by early experience and training (60). In designing

rehabilitation therapy, it should be noted that certain therapies or treatments used routinely in some rehabilitation settings could result in the formation of inappropriate connections and the prevention of functional recovery, even a form of learned helplessness (61). For instance, if the current paradigm of structure-function relationships is valid, it is hard to imagine how the capture of auditory input by visual fibers would automatically lead to an adaptive outcome.

In conjunction with electrophysiological experiments in primates, computer-assisted rapid fMRI studies in humans have shown that multiple systems throughout the brain become activated during selected cognitive tasks such as naming objects or performing simple mathematical calculations. Many neuroscientists now accept the view that widely distributed neural modules are involved in even simple cognitive or sensory processing. However, there is much less agreement as to the number of modules (brain areas) required to mediate even a simple behavior like reaching for a small piece of food. For example, over a period of about ten years, the number of CNS structures in the network said to be in control of 'vision' has increased from about 12 to well over 50. A corollary of this assumption is that highly focalized damage would cause very widespread changes both serially and in parallel throughout the brain. Therefore, recovery of behavioral functions may depend upon equally widespread changes in synaptic connectivity and their metabolic consequences.

### WHAT HAVE WE LEARNED FROM CONSIDERING THE CONCEPTUAL ISSUES SURROUNDING NEURAL "PLASTICITY"?

"Those who forget history are condemned to repeat it" means as much in neuroscience as it does in political and social philosophy. Theories and hypotheses now in vogue rarely acknowledge early twentieth-century literature pleading for more acceptance of a dynamic and modular view of function to replace the idea that the adult nervous system is fixed and immutable in its structure-function relationships. In particular, in the 1960s, 1970s, and 1980s, many neurobiologists, dependent on molecular and reductionistic techniques, seemed to take pleasure in deriding the ideas of Karl Lashley, who wrote in 1937 that "the function of cells may be deduced from their position and connections, but their position is not therefore a necessary consequence of their function." Lashley goes on to say that "the mere existence of specialized regions in the brain is not conclusive evidence that the specialization is necessary or important for the integrative functions" (62). Given the subsequent observations of reorganizational changes in response to brain injury that we have discussed,

Lashley's position now has a contemporary ring. Writing just two years later, Goldstein (63), a German neurologist, stressed that

the destruction of one part of the brain never leaves unchanged the activity of the rest of the organism, especially the rest of the brain. On the contrary, there usually occurs a widespread change of the distribution of excitation. Whether a certain symptom will appear on account of a local injury, especially whether it will become a permanent symptom, certainly depends on many other factors: the nature of the disease process, the condition of the rest of the brain, the difficulty of the performance requirements and the reaction of the entire organism to the defect. The localization of a performance (after an injury) no longer means an excitation in a certain place, but a dynamic process which occurs in the entire nervous system, even in the whole organism (pp. 258–259).

Thirty years after Goldstein, Alexander Luria argued that "the facts suggest that a disturbance of a particular form of activity may arise in far more extensive lesions than was hitherto supposed. Consequently, the performance of a given function necessitates the integrity of far more extensive and far more structurally varied zones of the cortex than was assumed by classical neurology" (51). Thus, almost four decades ago, Luria was arguing for a more dynamic view of nervous system function to account for how recovery from brain injury might occur. Luria felt it would eventually be recognized that "complex forms of psychological functions are never localized in isolated areas of the brain, but are always dependent on entire working constellations of cerebral zones, appearing in the course of postnatal development and changing dynamically as a particular functional system reaches a higher level of development." He predicted that the loss of any one link must inevitably lead to a disturbance of the normal working of the functional system as a whole (p. 70).

Luria's views were essentially ignored by the cerebral cartographers, who continued to add to the complexity of their diagrams without much concern for understanding how the parts worked together in the intact and the damaged brain. It was as if drawing the lines between anatomical components was a sufficient explanatory tool. Fortunately this view, so inimical to understanding the inherent plasticity of the CNS, is now being reconsidered in some quarters, although it is still far from extinction.

It must be said that contemporary research on localization of complex functions to specific areas of the cerebral cortex marshals some of neuroscience's most elegant techniques in support of its paradigm. This often entails careful testing of complex behaviors or components of behaviors while using microelectrodes to record

from specific cells in anatomically defined loci. Testing for speech generation or cognitive responses in humans often uses highly sophisticated imaging techniques. Some of the most elegant work in this domain has been performed by Goldman-Rakic and her colleagues, who have focused on defining and elaborating the role of the prefrontal cortex in spatial performance, memory and cognition. Goldman-Rakic's work investigates the hypothesis that highly discrete areas of the frontal cortex are critical in the mediation of spatial and object cognition (64–67). Monkeys show significant increases in electrophysical activity in individual neurons in circumscribed areas of the prefrontal cortex. During object recognition, one set of neurons is activated, while in a spatial cognition task other cells in a different anatomical region become more active. Both electrophysiological and metabolic recording techniques are used to demonstrate changes in activity. In Goldman-Rakic's view, "a signal advance attributable to research in non-human primates over the past decades has been the fine-grained functional mapping of the cerebral cortex and the realization that cytoarchitectonically defined areas are not homogenous with respect to circuitry or to physiology . . . . It is to be confidently expected that functional specializations will surely follow the lines of these anatomical divisions when the appropriate tests are applied." She concludes, "In view of the parcellation of these fundamental information processing domains, it is far too early to reject cortical specialization so well grounded in cytoarchitectonic, hodological and neurochemical parcellation . . ." (64). To be sure, the rigorous and refined techniques employed and the elegance of the results make for very compelling support for the doctrine of localization, but such findings and interpretations do not allow for the plasticity and reorganization seen after injury and are difficult to explain in the context of behavioral sparing or recovery of function in the adult organism. Studies not supporting parcellation theory are often dismissed as lacking technical sophistication or as having inappropriate behavioral tests.

Moreover, where plasticity of function is acknowledged it is often limited to the idea that immediately adjacent *cortical* tissue can be reorganized to mediate behaviors. Wall and Wang refer to these notions as "cortico-centric theories," because plasticity is thought to be limited primarily to cortical structures, where the most dynamic changes in maps are registered (67). In a more radical approach, these authors argue that changes in response to injury are far more ubiquitous in both subcortical and cortical substrates and include molecular, morphological, neurochemical and anatomical changes that reorganize basically the entire functioning of the organism. The authors take a position similar to that of the neurologists of the mid-twentieth century, who believed that the deficits as well as the recovery seen were

the result of such total organization, rather than the result of loss of a particular part in the brain.

In response to injury initial multilevel changes emerge surprisingly rapidly. Functional changes can appear concurrently within minutes in spinal, brainstem, thalamic and cortical substrates. With the passage of time during the subsequent days, weeks, months and longer, acute changes in normal substrates apparently continue, spread and are further supplemented by subcortical and cortical abilities to regenerate and sprout new connections (pp. 204–205).

The perspective of Wall et al. is consistent with the earlier work of Jones (68) and Nudo (58). Jones presents evidence that even very small changes in subcortical organization caused by a peripheral or CNS injury can lead to highly amplified changes in the organizational maps of the cerebral cortex. Others such as Chen et al. (69) argue that the brain is constantly being modified by experience and that 'pre-determined' wiring diagrams do not represent the kinds of rapid and long-lasting injury-induced plasticity seen in developmental and adult brain damage. The authors also note that not all types of reorganization are beneficial and that one must distinguish between those changes that lead to recovery and those plastic changes that result in permanent impairments.

Although not always given the credit they deserve, the early investigators into plasticity of function—Lashley, Goldstein, Luria—had only their clinical and observational skills to evaluate patient behavior and draw conclusions that today are based on a wide variety of sophisticated molecular and physiological techniques. Nonetheless, their conclusions resonate well with those of contemporary neuroscientists.

For example, considering his own work on phantom limb plasticity, Ramachandran (54) concluded that new findings (on reorganization after amputation) "allow us to test some of the most widely accepted assumptions of sensory psychology and neurophysiology, such as Müller's law of specific nerve energies, 'pattern coding' versus 'place coding' (i.e., the notion that perception depends exclusively on which particular neuron fires rather than the overall pattern of activity)." Furthermore, the work showing that sensations associated with phantom limbs by training "suggests that the modular, hierarchical 'bucket brigade' model of the brain popularized by computer engineers needs to be replaced by a more dynamic view of the brain in which there is a tremendous amount of back-and-forth interaction between different levels in the hierarchy and across different modules" (p. 319). Finally, with respect to motor cortex damage, Nudo et al. (58) conclude their review of the literature by stating that "both human and animal studies have demonstrated both acute and chronic changes in functional topography and anatomy of intact cortical tissue adjacent to the injury,

and of more remote cortical areas, including those of the contralateral (uninjured) hemisphere” (p. 1013).

Recent findings and the revised concepts of how adaptive and maladaptive plasticity occur in the adult human brain after injury clearly demonstrate that the adult CNS is capable of much more dynamic change in function and structure than had been thought over the last few decades of research in this area.

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# 10

## Advances in Innovative Therapies to Enhance Neural Recovery

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**T**his chapter reviews experimental neuroprotective agents, which are strictly defined as such if they have been reported to reduce morphological and/or functional deficits after traumatic brain injury (TBI). The categories below are not necessarily mutually exclusive. The pathways to cell dysfunction and death are not necessarily linear, but involve an intertwined network. The discussion also focuses on exogenous treatments rather than genetically induced manipulations (i.e., transgenic modification). Lastly, there will be no distinctions made between the various contemporary TBI models (1), although it is possible that the neuroprotective effects of some treatments may be model dependent.

### EXCITOTOXICITY

Excitotoxicity is an important mechanism in secondary neuronal injury following TBI. Glutamate, aspartate, and glycine are amongst the most abundant excitatory neurotransmitters and the most commonly implicated in excitotoxic injury. Glutamate, the most prominent of these amino acids, activates receptors that are classified according to specific agonists. Receptors that modulate ionic channels are divided into those stimulated by N-methyl-D-aspartate (NMDA receptors) or those stimulated by

$\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) or kainic acid (together referred to as non-NMDA receptors). Glutamate also acts at metabotropic receptors that act via second messenger systems (2). Excitotoxicity resulting from the TBI-induced release of excitatory amino acids and the damaging effects of increased intracellular calcium associated with glutamate receptor activation has been the target of intense investigation for over a decade.

### Inhibiting Release of Excitotoxins

Inhibiting glutamate release has been demonstrated to attenuate functional and morphological deficits after experimental TBI. Sun and Faden (3) reported that early treatment with 619C89, a sodium channel blocker that inhibits glutamate release, attenuates behavioral deficits and hippocampal neuronal loss. Riluzole (2-amino-6-trifluoromethoxy benzothiazole) has properties that include inhibition of glutamate release and has also been reported to attenuate functional (4) and morphological damage (5) after TBI. Treatment with galanin, a neuropeptide that inhibits neurotransmitter release by opening potassium channels and closing N-type calcium channels, attenuates motor, but not Morris water maze (MWM) deficits after TBI (6). However, blocking post-injury ion fluxes with tetrodotoxin was not found to be protective against behavioral deficits (7).

### Blocking Receptor Activation

As summarized below, treatment with NMDA and non-NMDA receptor blockers has led to improved functional recovery and reduced hippocampal cell death and cortical damage after experimental TBI. NMDA-receptor blockade has been shown in several models of TBI to attenuate neurological deficits. Hayes et al. (8) reported behavioral protection by the noncompetitive NMDA antagonist phencyclidine after TBI. Studies by Faden et al. (9) found behavioral protection by dextromethorphan, a noncompetitive NMDA antagonist and 3-(2-carboxypiperazin-4-yl)propyl-l-phosphonic acid (CPP), a competitive NMDA antagonist. The NMDA-antagonist, MK-801, has been reported in numerous studies to be neuroprotective (10–13). Cortical and hippocampal damage is attenuated by both pretreatment with the NMDA antagonist CPP and the non-NMDA antagonist NBQX (14). Additionally, delayed treatment with NBQX, but not CPP, beginning 1 and 7 hr after TBI prevented hippocampal damage.

Remacemide hydrochloride, an NMDA receptor-associated ionophore blocker, has been reported to reduce post-traumatic cortical lesion volume, but not to improve MWM function (15). Gacyclidine, a noncompetitive NMDA receptor antagonist has been shown to attenuate neuronal death and deficits in MWM performance following frontal cortex contusion (16). Treatment with kynureate, an NMDA and non-NMDA antagonist, has been reported to attenuate hippocampal CA<sub>3</sub> neuronal loss after TBI (17). Animals treated with HU-211, a synthetic, nonpsychotropic cannabinoid that acts as a noncompetitive NMDA receptor antagonist has been reported to enhance motor function recovery after TBI (18). The NMDA antagonist ketamine has been demonstrated to attenuate post-injury neurological (19) and cognitive deficits (20). Treatment with CP-98,113, an NMDA receptor blocker, has been shown to attenuate neurologic motor function and cognitive performance assessed in a MWM task (21). Increasing inhibitory function through stimulation of  $\gamma$ -aminobutyric acid (GABA(A)) receptors via bicuculline administration has been reported to attenuate MWM deficits after TBI (22).

In addition to playing an essential role in normal cell function, magnesium also has an antagonist effect on the NMDA receptor by blocking the NMDA receptor ion channel. The effects of magnesium after experimental TBI are presented in the “neutraceuticals” section of this chapter.

Many noncompetitive NMDA receptor antagonists have undesirable side effects. NPS 1506 is a noncompetitive NMDA receptor antagonist that appears less toxic than earlier agents (23). NPS 1506 has been reported to attenuate MWM performance and hippocampal CA<sub>3</sub> cell death, but not cortical lesion (23).

TBI-induced glutamate release can also damage tissue by activating metabotropic glutamate receptors

(mGluR), which are coupled to second messenger cascades through G-proteins. Modulation of mGluRs has been shown to confer neuroprotection. Gong et al. (24) reported that intraventricular administration of  $\alpha$ -methyl-4-carboxyphenylglycine (MCPG), a mGluR antagonist, prior to TBI attenuated motor and MWM deficits. Administration of 2-methyl-6-(phenylethynyl)-pyridine (MTEP), a mGluR5 antagonist, has been reported to reduce lesion volume and to attenuate motor and MWM deficits following TBI (25). Administration of a group II mGluR agonist 30 min after TBI can improve behavioral recovery (26). Selective mGluR1 antagonists have also been reported to attenuate motor deficits and MRI-assessed lesion volume (27). The compound ZJ-43, which inhibits N-acetylaspartylglutamate through selective activation of presynaptic Group II mGluR3, has been recently shown to attenuate neuronal and glial degeneration after TBI (28).

### Calcium Channel Blockers

Calcium channel blockers to reduce excessive accumulation of intracellular calcium have been examined as possible neuroprotective agents for TBI. Post-injury administration of the voltage-sensitive calcium channel blocker Ziconotide (also SNX-111 and CI-1009) has been reported to attenuate motor and cognitive deficits (29). Similarly, post-injury treatment of LOE 908, a broad-spectrum inhibitor of voltage-operated cation channels and store-operated cation channels has been demonstrated to reduce neuromotor and visuospatial memory deficits (30). Recently, treatment with the specific N-type voltage-gated calcium channel blocker SNX-185 has been shown to attenuate functional deficits and enhance neuronal survival after TBI (31). Pharmacologically blocking calcium entry has been another important strategy to reduce post-injury excitotoxicity. Treatment with (S)-emopamil, a calcium channel blocker, has been reported to attenuate post-injury motor deficits (32). Inhibiting polyamine-dependent calcium influx is another therapeutic target for attenuating post-injury excitotoxicity. Ifenprodil, a polyamine-site NMDA receptor antagonist, has been reported to reduce cortical morphology after TBI (33).

### OXIDATIVE INJURY

Oxidative stress has been implicated in the pathology of TBI. Several agents with antioxidant properties have been evaluated in animal models of TBI. Hall and colleagues (34) reported that administration of a non-glucocorticoid 21-aminosteroid U74006F (tirilazad) enhanced neurological recovery in mice. Tirilazad has also been reported to attenuate axonal injury following TBI (35). Clifton et al. (36) reported that pretreatment and acute posttreatment with

$\alpha$ -tocopherol succinate plus polyethylene glycol attenuated motor deficits following TBI. Analogues of  $\alpha$ -tocopherol have also been reported to be neuroprotective in mice following TBI (37). Lidocaine, a local anesthetic, has been found to be a potent scavenger of hydroxyl radicals (38). Administration of lidocaine has been reported to attenuate postinjury neurological and motor function, but not cognitive function (39). Deferoxamine is an iron-chelating agent that can inhibit the iron-dependent hydroxyl radical production, and has been reported to improve spatial memory performance following TBI (40). Interestingly, deferoxamine was found not to improve functional outcome when combined with moderate hypothermia treatment (41). Superoxide dismutase (SOD) is a metalloenzyme, which catalyzes the dismutation of superoxide ion into oxygen and hydrogen peroxide. Administration of polyethylene glycol-conjugated SOD has been reported to reduce motor, but not MWM deficits following TBI (42). OPC-14117, is a superoxide scavenger that has been reported to attenuate tissue damage (43) and behavioral deficits (44,45) following TBI. Early treatment with LY341122, an inhibitor of lipid peroxidation and an antioxidant, has been reported to provide significant histopathological protection (46). Penicillamine is a scavenging compound that has been reported to improve motor performance in mice after TBI (47). The pineal hormone melatonin is a scavenger of free radicals has been found to reduce contusion volume following cortical impact in rats (48). Endothelin-1, a 21 amino acid peptide, has been closely linked to oxidative stress after TBI (49). The endothelin receptor subtype A antagonist, Ro 61-1790 has been shown to attenuate Purkinje cell loss in the cerebellum after TBI. Kline and colleagues have recently shown that acute administration of the dopamine D2 receptor agonist bromocriptine, which exhibits significant antioxidant properties, reduced TBI-induced lipid peroxidation (i.e., oxidative stress) and enhanced spatial learning in a MWM task and increased hippocampal CA3 neuron survival after controlled cortical impact injury (50).

## EXOGENOUS GROWTH FACTORS

Exogenous administration of several growth factors has been reported to produce beneficial effects on both cognitive performance and histological outcome measures after TBI. Sinson and colleagues have shown that nerve growth factor (NGF) attenuates cognitive dysfunction following fluid percussion brain injury (51). The same group has also reported an attenuation of cognitive deficits and cholinergic cell loss after fluid percussion injury and NGF infusion (52). Dixon et al. (53) have reported that intraventricular NGF infusion reverses the post-traumatic reduction in scopolamine-evoked ACh release, and significantly improves spatial memory retention following

controlled cortical impact injury. Increasing NGF protein levels by intraventricular injections of liposome/NGF cDNA complexes similarly attenuates the loss of cholinergic neuronal immunostaining in the rat septum after TBI (54).

Utilizing the fluid percussion injury device, Frank and Ragel (55) demonstrated via histochemical quantification that at 48 hr after injury there is a significant difference in FGF-2-positive cells between the injured and contralateral cortex. Dietrich et al. (56) administered fibroblast growth factor-2 (FGF-2) intravenously for 3 hr beginning 30 min after fluid percussion injury and found a 50 percent decrease in the total number of necrotic neurons compared to controls. Furthermore, the overall contusion lesion volume was decreased by almost a third. Employing the same injury model, McDermott and colleagues (57) reported that post-injury FGF-2 treatment significantly attenuated post-traumatic memory dysfunction relative to vehicle-treated controls. However, no attenuation in histological damage was observed. In contrast to the beneficial effects reported by Dietrich et al. (56) and McDermott et al. (57) with FGF-2 treatment after fluid percussion injury, Guluma and colleagues failed to see a neurological improvement at 7 days after an injury of moderate severity in a similar same model (58). Using the controlled cortical impact injury model in rats, Yan and colleagues have shown that FGF-2 administration moderately improves MWM performance compared to controls, but has no effect on histological outcome (59). Recently, Yoshimura and colleagues reported that overexpression of FGF-2 increases neurogenesis in the adult mouse hippocampus after cortical impact injury and that neurogenesis is reduced in FGF-2 deficient mice (60). The authors conclude that supplementation of FGF-2 may be effective in treating TBI by simultaneously enhancing neurogenesis and reducing neurodegeneration.

Insulin-like growth factor 1 (IGF-1) is a mitogenic polypeptide structurally similar to insulin that is involved in repair and regeneration following injury to the brain. IGF-1 has been shown to be upregulated following cerebral cortical contusion via a weight drop injury model (61). A follow-up study found that the upregulation of IGF-1 mRNA levels can be blocked by NMDA receptor antagonists (62). Exogenous administration of IGF-1 has been demonstrated to improve neurological and cognitive outcome after fluid percussion brain injury in rats (63). IGF-1 has recently been evaluated in a unilateral penetration brain injury model. IGF-1 administration resulted in a significant decrease in Hsp70 and TUNEL positive cells in the peritrauma region. The neuroprotective effects of IGF-1 treatment were not limited to the cellular level, but also on behavioral outcome. Specifically, IGF-1 treated animals lost less postoperative weight and survived the trauma longer than controls (64).



## HYPOTHERMIA

During the past decade, several experimental studies have provided evidence that mild to moderate hypothermia can provide behavioral protection following TBI. Studies employing multiple models have reported that moderate hypothermia can reduce neurological deficits (65–69) and improve cognitive function (59,65,67,69). Reports of histological protection by moderate hypothermia have been less consistent. Some investigators have reported reductions in contusion volume (70,71) decreased cortical necrotic neurons (70), reductions in axonal injury (72), and reduced ventricular enlargement (73). However, in a rat model of severe TBI with secondary insult, moderate hypothermia for 4 hr post-injury failed to improve motor function, cognitive function, lesion volume, or hippocampal neuronal survival (74). Furthermore, moderate hypothermia was found to be detrimental in fentanyl-anesthetized rats (75). Factors such as treatment window, injury severity, anesthesia, and rates of re-warming need to be further defined to optimize hypothermia treatment. (See Figure 10-1.)

## PROTEASE INHIBITORS

Both intracellular proteases (e.g., calpains and caspases) and extracellular proteases (plasminogen activator and matrix metalloproteinase) are believed to contribute to the pathophysiology of neuronal cell death (76). Treatments that target these processes have been evaluated in experimental TBI. Post-injury uncontrolled activation of calpain, a calcium-dependent neutral protease, can destroy neurons. Calpain inhibitors have been the most researched target for TBI treatment. (Caspase inhibitors are reviewed below.) Saatman et al. (77) reported that treatment with the calpain inhibitor AK245 attenuated motor and cognitive deficits following TBI. A follow-up study found that AK245 did not attenuate cell death (78). Treatment with calpain inhibitor 2 has been demonstrated to reduce cortical loss following TBI (79). Administration of the calpain inhibitor SJA6017 has been found to inhibit functional deficits 24-hr postinjury (80). Treatment with the nonimmunosuppressive neuroimmunophilin (NIMM) ligand V-10,367 has been found to reduce calpain-mediated cytoskeletal damage (81). It has been recently

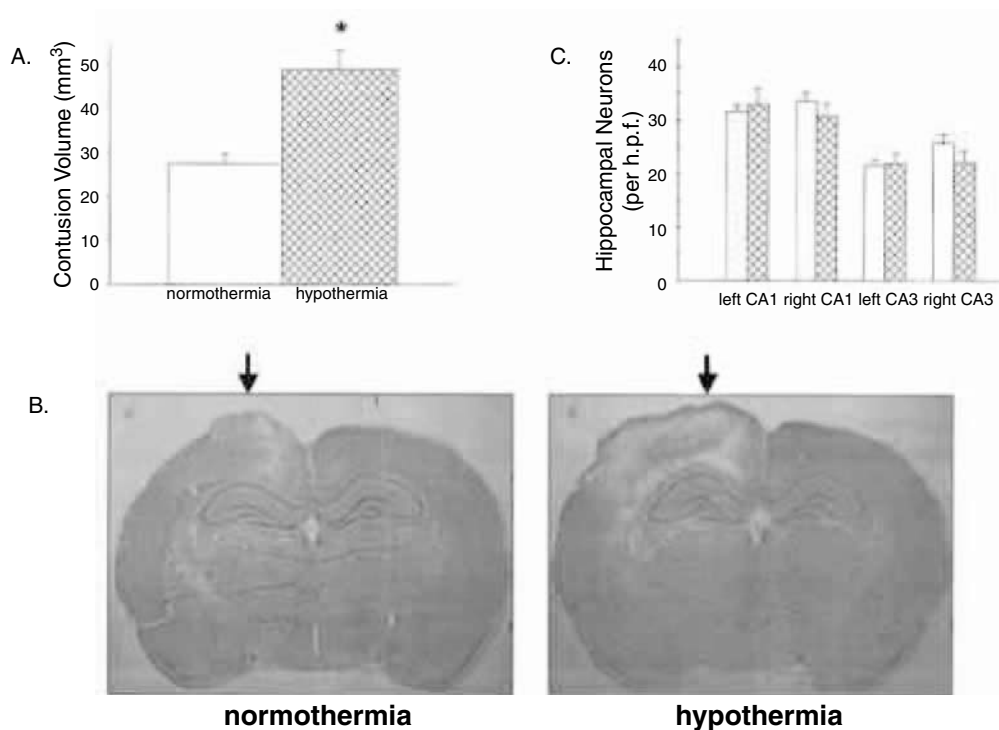


FIGURE 10-1

Histologic assessment performed 72 hr after traumatic brain injury in rats ( $n = 8$  per group) treated with normothermia vs. hypothermia. **A**, surprisingly, contusion volume was markedly larger in hypothermic rats ( $*p < 0.05$ ). **B**, representative coronal brain sections. The site of impact is marked by arrows. Contusion volume, demarcated by swollen, hypochromic cells, was nearly doubled in hypothermic rats. The hippocampus appeared largely unaffected in both experimental groups. **C**, hippocampal neuronal survival did not differ between experimental groups. Controlled cortical impact was delivered to the cortex overlying the left dorsal hippocampus. [From Statler et al., *Crit Care Med*, 2003; 31(4):1134–1139 (Ref. 75).]

demonstrated that preinjury administration of the calpain inhibitor MDL-28170 significantly reduced immunomarker of axonal injury after TBI (82).

### INFLAMMATION

TBI can initiate a number of inflammatory processes that may contribute to secondary tissue damage. For instance, TBI can produce polymorphonuclear leukocyte migration into the brain that can result in neuronal damage. P-selectin blockade has been reported to reduce probe trial performance on a MWM task following TBI (83). Knobloch and Faden (84) demonstrated that anti-intracellular adhesion molecule-1 (ICAM-1) can attenuate motor deficits and neutrophil invasion after TBI. Systemic administration of a high, but not a low dose of interleukin-1 receptor antagonist has been reported to attenuate neurological recovery after TBI (85). The same study observed that motor function was impaired by the high dose of interleukin-1 receptor antagonist (85). Further work by Knobloch and Faden (86) failed to find a beneficial effect of selective IL-1 antagonists and suggested that the post-traumatic increases in IL-1-beta may not contribute to subsequent neurological impairment. Administration of anti-CD11B, a monoclonal antibody directed against the leukocyte adhesion molecules CD11B, reduced neutrophil influx after TBI, but did not improve function (87). Nitric oxide (NO) derived from the inducible isoform of NO synthase (iNOS) is an inflammatory product implicated both in secondary damage and in recovery from brain injury. Sinz et al. (88) reported that rats treated with iNOS inhibitors aminoguanidine and L-N-iminothyl-lysine exacerbated functional outcome and histological damage thereby suggesting a beneficial role for iNOS in TBI. In contrast, Lu et al. (89) found that aminoguanidine treatment improved neurobehavioral outcome. Acute administration of a selective iNOS inhibitor, 1400W, has been shown to reduce lesion volume after lateral fluid percussion injury (90). Treatment with interleukin-10 has been reported to enhance neurological recovery following fluid percussion brain injury (91). However, the administration of interleukin-10 thirty min after experimental TBI via a controlled cortical impact was ineffective in attenuating functional and histopathological deficits with a dose that prevents neurotrophil accumulation in injured tissue (92). Cyclooxygenases (COX) play an important role in inflammatory cascades and increased expression of COX after experimental TBI has been well documented (93–96). Cernak et al. (95) found that chronic administration of the COX-2 inhibitor nimesulide improves cognitive function after TBI. Pre- and post-injury treatment with DFU has been shown to attenuate functional deficits and neuronal cell death after controlled cortical impact (97). At present, anti-inflammatory treatments remain a viable strategy.

### ETHANOL

The neuroprotective effects of ethanol have been disputed for years. Yamakami et al. (98) demonstrated that following severe brain injury, animals pretreated with high-dose ethanol showed significantly worsened neurological deficits at 24 hr postinjury. Shapira et al. (99) reported that acute, but not chronic, ethanol exposure increased neurological deficit and hemorrhagic necrosis volume in rats following TBI. Janis et al. (100) reported that low dose acute ethanol treatment could reduce MWM performance deficits. A low-dose of ethanol has been found to be associated with a marked attenuation of immediate post-injury hyperglycolysis and with more normal glucose metabolism in the injury penumbra over the ensuing 3 days post-injury (101). It was further observed that the reduction in CBF typically seen within the contusion core and penumbra after TBI is less severe when ethanol is present. In contrast, in a model of multiple episodes of mild TBI, acute ethanol intoxication acute ethanol treatment was not neuroprotective in rats (102). Acute pre-injury administration of ethanol has been shown to attenuate the cytokine response to injury (103). Recently, a treatment consisting of a low amount of ethanol combined with caffeine (caffeinol), has been found to be neuroprotective (104). If there is a beneficial effect of ethanol, the conditions by which it can be neuroprotective remain to be clarified.

### HORMONAL AND GENDER INFLUENCES

It has been postulated in animal studies that the effects of female hormones may play a positive role in outcome from brain injury. Roof et al. (105) found that the presence of circulating endogenous or synthetic progesterone had a neuroprotective effect on the reduction of cerebral edema in female rats compared to males. However, in a temporal response study, Galani et al. (106) found that a 4 mg/kg dose of progesterone was more effective in reducing edema after medial frontal cortex contusions when given for 5 consecutive days versus 3 days. The authors speculate that the longer duration of progesterone treatment was more effective because there are two phases of edema—one that begins within hr after trauma and another that begins several days later (106). Apparently, the longer treatment was able to effectively attenuate the later phase of edema. In a similar study from the same group, 5 days of progesterone treatment was shown to protect against necrotic damage and behavioral abnormalities (107). Progesterone has also been reported to confer protection against lipid peroxidation and to facilitate cognitive recovery and reduce secondary neuronal loss after cortical contusion in male rats (105,108). It has recently been reported that allopregnanolone

(4,8, or 16 mg/kg), which is a metabolite of progesterone, and progesterone (16 mg/kg) administered at 1 and 6 hr after controlled cortical impact to the pre-frontal cortex and every day thereafter for 5 days resulted in less cell loss in the medio-dorsal nucleus of the thalamus and less learning and memory deficits compared with the vehicle-treated controls (109).

Animal studies also show that estrogen treatment immediately after TBI has a protective effect in males, but increases mortality and exacerbates outcome in females when assessing neurologic motor function one week after injury (110). Other studies (111,112) show a protective role of estrogen in maintaining cerebral blood flow, mortality, and cell death after experimental TBI. A recent study by Wagner et al. examined the effects of pre-injury hormonal status and gender on neurobehavioral and cognitive performance after controlled cortical impact injury. The results showed that females performed significantly better than males on motor performance measures, but were not significantly different on cognitive outcome as assessed in the MWM. Furthermore, there were no differences in performance between pro-estrous and non-proestrous females, suggesting that neither estrous cycle stage nor hormone level at the time of TBI have significant effects on behavioral recovery (113). These findings are supported by the results of a study in which nonovariectomized rats were subjected to a right parasagittal fluid percussion brain injury during either proestrous or nonproestrous and compared to ovariectomized female and male rats. Rats were sacrificed three days after TBI to assess neuropathology. The results showed that both the proestrous and nonproestrous rats had significantly smaller cortical lesions relative to males. In contrast, the ovariectomized females had contusion volumes that were significantly larger than both the proestrous and nonproestrous intact rats (114). Taken together, these data provide evidence that endogenous circulating hormones confer histopathological and behavioral protection after TBI.

### MITOCHONDRIA

Sequestration of calcium loads within the mitochondrial matrix can open the mitochondrial permeability transition pore leading to cellular oxidative and metabolic stress. Acute treatment with cyclosporin A (CsA), an inhibitor of calcium-induced mitochondrial permeability transition pore, has been reported to reduce tissue damage following TBI in rats (115–117). CsA has also been found to enhance cognitive function after TBI (118). A single dose of CsA has also been reported to blunt axonal damage following TBI (119). Continuous infusion of CsA after TBI has been found to reduce cortical damage (117). Improved mitochondrial function and

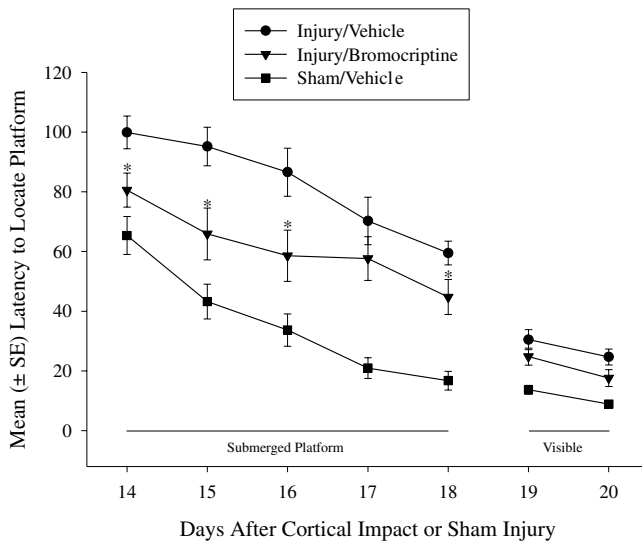
behavioral outcome has been achieved by treatment with ziconitide, a calcium channel blocker (120,121).

### CATECHOLAMINE AGONISTS

The role that catecholamines play in promoting functional recovery after TBI is well documented (122–127). Feeney and colleagues have shown that a single dose of d-amphetamine administered 24 hr after a sensorimotor cortex injury produces an immediate and enduring acceleration in beam walking recovery in rats (122) and that multiple doses of amphetamine restore binocular depth perception in cats with bilateral visual cortex ablation (128). Beneficial effects of other catecholamine agonists on functional outcome in rat and/or cat following either weight drop cortical contusion or cortical aspirations have also been reported (129). Because the administration of norepinephrine antagonists block or reinstate deficits, the noradrenergic system has been implicated in the aforementioned studies. However, as suggested by the following reports, the dopaminergic system is also involved in the rehabilitative process.

The psychostimulant methylphenidate has been reported to have pharmacological properties similar to amphetamine, but without the undesirable sympathomimetic effect. A single administration followed by significant symptom relevant experience (i.e., beam walking experience) enhances recovery of motor function following sensorimotor cortex lesions (126). Moreover, daily methylphenidate treatments beginning as late as 24 hr after TBI in rats reveal significantly less spatial memory performance deficits versus saline treatment (127). Recently, the effect of daily administrations of amantadine beginning one day post-injury and continuing for 20 days was examined. Rats treated with amantadine had significantly less spatial memory performance deficits than their saline-treated counterparts (130). Biochemical studies have demonstrated that amantadine increases release of DA into extracellular pools by blocking reuptake and by facilitating the synthesis of DA (131–134). In addition to acting pre-synaptically, amantadine has been demonstrated to act post-synaptically to increase the density of post-synaptic DA receptors (134) or to alter their conformation (135). Evidence of a post-synaptic mechanism is clinically promising since the mechanisms of actions may not depend solely on the presence of surviving post-synaptic terminals. Because the mechanism of action of amantadine differs from other DA releasing drugs (see 136 for review), it is likely that the dopaminergic effects of amantadine are a combination of pre-synaptic and post-synaptic effects.

Rats receiving delayed and chronic pharmacological treatment with the dopamine D<sub>2</sub> receptor agonist bromocriptine exhibited both enhanced working memory



**FIGURE 10-2**

Mean ( $\pm$  SE) latency (sec) to locate a submerged platform in a spatial learning acquisition paradigm. \* $P < 0.05$  vs. injury/vehicle. [From Kline et al., *J Neurotrauma* 2002; 19:415–425 (Ref. 50).]

and spatial acquisition in a MWM. Specifically, both injured groups exhibited significant impairments initially, but in marked contrast to the performance of the vehicle-treated group, the bromocriptine-treated animals required significantly less time to locate the platform (50). The dose of 5 mg/kg bromocriptine has been shown via microdialysis to increase extracellular DA levels in rats (137), suggesting that enhanced DA neurotransmission mediated the beneficial effects. However, as indicated in the “oxidative injury” section, the same dose of bromocriptine has also been reported to attenuate lipid peroxidation, suggesting that bromocriptine’s antioxidant properties may also contribute to its therapeutic effects (50). (See Figure 10-2.)

The administration of selegiline (L-deprenyl) once daily for seven days beginning 24 hr after fluid percussion injury has been reported to improve cognitive function in the MWM and enhance neuroplasticity (138). L-deprenyl is used to enhance the action of DA by inhibiting its main catabolic enzyme in the brain, monoamine oxidase-B. Clinical studies also exist attesting to the benefits of DA augmentation following TBI (139,140).

These positive finding with delayed treatment suggests that strategies that enhance catecholamine neurotransmission during the chronic post-injury phase may be a useful adjunct in ameliorating some of the neurobehavioral sequelae following TBI in humans.

## SEROTONIN AND TBI

Investigations regarding the role of serotonergic (5-HT) responses after TBI have not been as prolific as with other

neurotransmitter systems. Utilizing a fluid percussion rat brain injury model, Busto et al. (141) reported that 5-HT levels increased from  $18.85 \pm 7.12$  to  $65.78 \pm 11.36$  pm/ml (mean  $\pm$  SD) in the first 10 min after injury. The levels of 5-HT remained significantly higher than controls for the first 90-min sampling period. In parallel to the rise in 5-HT levels a significant 71 percent decrease in extracellular 5-HIAA levels was noted in the first 10 min after injury. These findings suggest that there is a rapid rise in extracellular 5-HT levels in cortical regions proximal to the injury site. Because 5-HT potentiation of excitatory amino acids has been reported in cat neocortex (142), the trauma-induced release of 5-HT might negatively impact recovery by promoting excitotoxic processes.

Serotonergic pathways originating in the raphe nuclei have extensive projections to brain areas involved in cognitive processing, and 5-HT receptor agonists and antagonists alter these processes (143,144). Of all the 5-HT receptors (5-HT<sub>R</sub>) characterized thus far (5-HT<sub>1</sub>–5-HT<sub>7</sub>), the 5-HT<sub>1A</sub> is the most widely studied. 5-HT<sub>1A</sub>Rs are abundantly expressed in brain regions, such as the cortex and hippocampus, that play key roles in learning and memory and that are susceptible to neuronal damage induced by brain injury (145,146). Numerous studies have reported on the effects of 5-HT<sub>1A</sub>R agonists after focal or global cerebral ischemia in both rats and mice (145–150). These studies have focused on either pre or post-injury administration of various 5-HT<sub>1A</sub>R agonists and their potential neuroprotective effects. What is generally found is that 5-HT<sub>1A</sub>R agonism decreases histopathology after ischemic injury.

The investigation of 5-HT<sub>1A</sub>R agonists on neurobehavioral and cognitive recovery after TBI produced by a well-established controlled cortical impact injury model, which produces deficits resembling those seen clinically, has only recently begun. Kline and colleagues have shown that a 4-hr continuous infusion of Repinotan HCL (BAY  $\times$  3702; 10  $\mu$ g/kg/hr i.v.), a high-affinity, highly selective 5-HT<sub>1A</sub>R agonist, commencing 5 min after cortical impact produced a marked attenuation of TBI-induced learning and memory deficits assessed in the MWM. Moreover, this treatment regimen attenuated hippocampal CA<sub>1</sub> and CA<sub>3</sub> cell loss, and decreased cortical lesion volume relative to vehicle-treated controls (151). Utilizing the same TBI model, Kline et al. (152) have also demonstrated that the classic 5-HT<sub>1A</sub>R agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) produces similar effects on functional and histological outcome. Briefly, in a dose response study, a single dose of 0.5 mg/kg administered intraperitoneally 15 min following cortical impact significantly attenuated water maze performance relative to the vehicle controls. Additionally, 8-OHDPAT attenuated hippocampal CA<sub>3</sub> cell loss. The administration of the 5-HT<sub>1A</sub> receptor antagonist WAY 100635 did not significantly impact functional or histological outcome following TBI. (See Figure 10-3.)

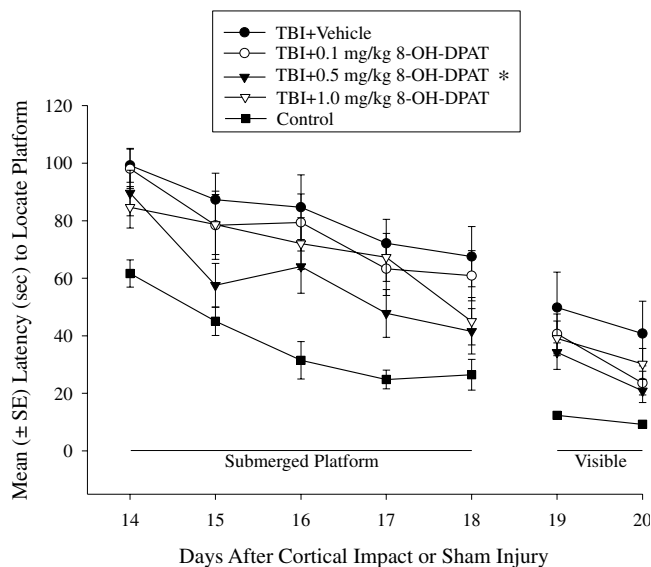


FIGURE 10-3

Mean ( $\pm$  SE) latency (sec) to locate either a submerged (hidden) or raised (visible) platform in a spatial learning acquisition paradigm in the Morris water maze. \* $P < 0.05$  vs. TBI+Vehicle (Scheffé). [From Kline et al., *Neurosci Lett* 2002; 333:179–182 (Ref. 152).]

Although potential mechanisms contributing to the beneficial effects observed after a single treatment with 8-OH-DPAT in our TBI paradigm have not been reported, the results from other studies investigating 5-HT<sub>1A</sub>R agonists suggest that it is via an attenuation of excitotoxicity. Electrophysiological studies have shown that 8-OH-DPAT, repinotan HCL, and other 5-HT<sub>1A</sub>R agonists induce neuronal hyperpolarization by activating G-protein coupled inwardly rectifying K<sup>+</sup> channels (153,154) and decrease glutamate release after brain insult (145, 147,148). The latter effect is likely produced by activation of pre-synaptic 5-HT<sub>1A</sub> receptors on glutamatergic terminals (155,156). 5-HT<sub>1A</sub>R activation may also contribute to neuroprotection by directly interacting with voltage-gated Na<sup>+</sup> channels to reduce Na<sup>+</sup> influx (157). 8-OH-DPAT and other 5-HT<sub>1A</sub>R agonists also induce hypothermia (157–160), which may be another potential mechanism contributing to the neuroprotective effects observed in our studies. As indicated in a separate section of this chapter, hypothermia is a potent neuroprotective strategy after brain injury. However, we have recently reported that the beneficial effects observed with a single and early intraperitoneal injection of 8-OH-DPAT is not mediated by concomitant hypothermia. Briefly, following TBI and 8-OH-DPAT administration (same dose, route, and time frame as in the previous study, (152), we controlled temperature (normothermia) in one group of 8-OH-DPAT treated rats and allowed the other group to cool spontaneously. A comparison of both 8-OH-DPAT treatment groups did not reveal a difference in functional

or histological outcome, but both did perform significantly better than the vehicle control group (161).

## ACUTE CHOLINERGIC TREATMENT

Acetylcholine (ACh) levels have been reported to change in brain and cerebral spinal fluid (CSF) following TBI. Gorman et al. (162) reported that hippocampal ACh levels (measured by microdialysis) increased significantly above control within 10 min after fluid percussion TBI. Saija et al. (163,164) found that ACh turnover rate (measured by a phosphoryl [<sup>2</sup>H<sub>5</sub>]choline method) increased significantly in the brainstem at 12 min and was still elevated at 4 hr after moderate fluid percussion TBI in the rat. Thus, moderate TBI appears to produce a transient release of ACh and increased cholinergic neuronal activity in some brain regions for several hr after injury.

Laboratory studies have demonstrated that excessive activation of acetylcholine (ACh) muscarinic receptors contribute significantly to functional deficits associated with experimental TBI in the rat. TBI induced muscarinic receptor activation mediates excitotoxic processes by modulating ionic fluxes via altered protein kinase C activity or inositol 1,4,5-triphosphate associated G-protein coupled PI turnover. The role of ACh in the induction of brain injury is further strengthened by evidence indicating that blockade of muscarinic cholinergic receptors during the acute phase can reduce injury and improve outcome. For example, pre-treatment (165,166) or immediate post-treatment (166) with the muscarinic receptor antagonist scopolamine has been demonstrated to significantly reduce functional motor deficits associated with TBI in the rat. Post-TBI administration of rivastigmine, an anticholinesterase drug that increases activity at both muscarinic and nicotinic receptors, has been shown to attenuate neurobehavioral and cognitive performance in mice.

In contrast, several lines of evidence indicate that experimental TBI in rats, in addition to transiently increasing ACh, also chronically decreases cholinergic neurotransmission, which may be related to disturbances in cognitive performance. Microdialysis studies at 2 weeks post-TBI have shown a reduction in the release of ACh evoked by the muscarinic autoreceptor antagonist, scopolamine (167,168). TBI can also produce increased sensitivity to disruption of spatial memory function by scopolamine that occurs concurrently with a reduction in scopolamine-evoked ACh release (169). A time-dependent loss of choline acetyltransferase (ChAT) enzymatic activity (162) and ChAT immunohistochemical staining (49,170,171) has also been reported after TBI. Dixon et al. (169) have reported a selective decrease in the  $V_{max}$  of choline uptake in the absence of any change in  $K_m$  after controlled cortical impact injury. However, alterations in synaptosomal choline uptake have not been

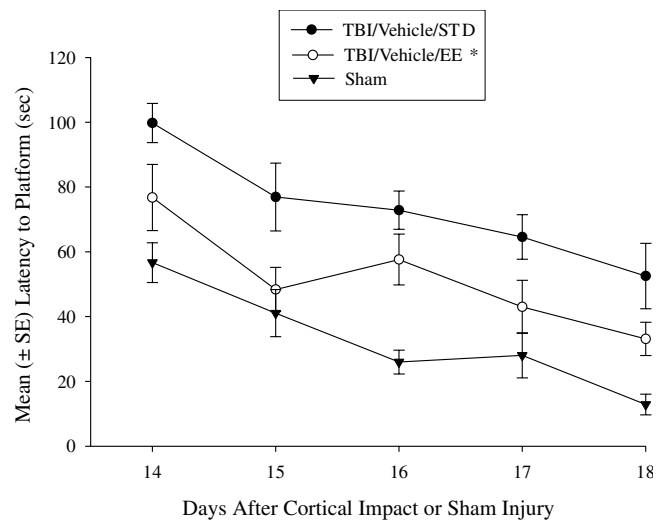
reported at 1 week after closed head impact in rats (172). Ciallella and colleagues have reported chronic changes in vesicular ACh transporter (VACHT) and M<sub>2</sub> cholinergic muscarinic receptor, two proteins involved in cholinergic neurotransmission after TBI (173). Chronic mRNA changes in VACHT and M<sub>2</sub> have been evaluated at 4 weeks after moderate brain trauma in rats. VACHT and M<sub>2</sub> medial septal mRNA levels evaluated by RT-PCR revealed an increase in VACHT mRNA, but no significant change in M<sub>2</sub> mRNA levels compared to sham controls (174). Changes in VACHT and M<sub>2</sub> protein have been demonstrated to persist for up to one year following TBI (175). These changes may represent a compensatory response of cholinergic neurons to increase the efficiency of ACh neurotransmission chronically after TBI through differential transcriptional regulation.

Increasing levels of ACh pharmacologically can attenuate post-traumatic spatial memory performance deficits. For example, increasing ACh synthesis by increasing the availability of choline using CDP-choline treatment has been reported to enhance spatial memory performance (176). Additionally, chronic post-TBI administration of BIBM 99, a selective muscarinic M<sub>2</sub> receptor antagonist that increases ACh release by blocking pre-synaptic autoreceptors, has been reported to attenuate spatial memory deficits after TBI (177). Similarly, chronic post-TBI administration of MDL 26,479 (suritazole), a negative modulator at the  $\gamma$ -aminobutyric acid (GABA) receptor that enhances cholinergic function, attenuates spatial memory deficits after TBI (178). Several clinical reports have described beneficial effects on memory dysfunction with the acetylcholine-esterase inhibitor aricept (donepezil) after TBI in humans (179–182). Taken together, the studies described in this section suggest that therapies that attenuate the transient increase in ACh and/or alleviate the chronic decrease seen after TBI are capable of producing beneficial effects on functional outcome.

## ENVIRONMENTAL ENRICHMENT

Exposing rats to complex, stimulatory and social housing (enriched environment (EE)) may be considered a rodent correlate of physiotherapeutic intervention and has been extensively studied in numerous experimental conditions. EE has been reported to increase brain weight, cortical volume, dendritic arborization, synaptogenesis, and neuronal survival (183,184). EE has also been shown to decrease apoptosis of neuronal precursor cells in the hippocampal dentate gyrus (185–187). Rats housed in EE for 30 days exhibit significantly higher levels of nerve growth factor mRNA in the rat visual cortex and hippocampus than those living in standard conditions (188). EE selectively increases 5-HT<sub>1A</sub> receptor mRNA

expression and binding in the rat hippocampus (189). This finding demonstrates the importance of 5-HT-receptor subtypes in the effects of housing environment on hippocampal functions, such as synaptic plasticity. EE has also been shown to increase the expression of brain-derived neurotrophic factor mRNA in the rodent hippocampus, which correlates with improved spatial memory (190). Somatostatin levels (191), glucocorticoid receptor, and the nerve growth factor-induced immediate early gene NGFI-A (192) are also increased following exposure to an EE. In contrast to the studies observing increases in gene and neurotrophic expression (193,194), Hicks et al. (195) did not see alterations in BDNF, TrkB, or NT-3 gene expression in lateral fluid percussion injured rats exposed to an EE, but did see an attenuation of cognitive deficits. Hamm et al. (196) also reported improved MWM performance in rats exposed to an environment consisting of objects that provided motor, olfactory, tactile, and visual stimulation for 15 days following moderate fluid percussion injury. Furthermore, rats exposed to EE for 11 days after severe fluid percussion injury demonstrated improved MWM performance and reduced contusion lesion volume (197). EE has also been demonstrated to improve motor performance on a beam walk task or sensory neglect after cortical lesions (198–200). Wagner and colleagues have recently demonstrated that placing rats in an EE immediately after controlled cortical impact injury facilitates cognitive function in a spatial learning and memory task in the MWM (201). Briefly, as depicted in Figure 10.4, the rats in the EE (i.e., large cage with toys and objects designed to provide enhanced sensory stimulation) performed significantly better than the rats in standard conditions



**FIGURE 10-4**

Mean ( $\pm$  SE) latency (sec) to locate a submerged platform in a spatial learning acquisition paradigm. \* $P < 0.05$  vs. standard conditions. [From Wagner et al., *Neurosci Lett* 2002; 334:165–168 (Ref .201).]

(i.e., 2 rats per standard [STD] size cage with no enhanced sensory stimuli). Taken together, these reports attest to the beneficial effects conferred by EE after brain injury. Further studies investigating the combined effects of EE and pharmacotherapies known to also provide benefit after TBI, such as those outlined in this chapter, are warranted to examine this potentially efficacious, and perhaps synergistic, therapeutic approach. (See Figure 10-4.)

### STEM CELL THERAPY

Multipotential stem cells are a contemporary choice for cell therapy TBI, as replacement of multiple cell types may be required for functional recovery. Several investigators have demonstrated that following TBI in adult rats, the number of proliferating cells labeled with bromodeoxyuridine is significantly increased in the bilateral subventricular zone and dentate gyrus (202–205). A better understanding of these endogenous neural stem cells may lead a less invasive model of stem cell therapy. There are several promising studies in which the transplantation of various progenitor cells have improved tissue survival and functional outcome. Bone marrow stromal cells, which normally give rise to bone, cartilage, adipose tissue, and hematopoiesis-supporting cells, have been shown to differentiate *in vitro* and *in vivo* into neural-like cells. Following TBI, treatment with bone marrow stromal cells has been shown to be functionally beneficial using intracerebral (206), intraarterial (207) and intravenous routes of administration (208). Transplantation of the neural stem cells (clone C17.2) has been reported to survive in the traumatically injured brain, differentiate into neurons and/or glia, and attenuate motor dysfunction after traumatic brain injury (209). Transplantation of embryonic stem cells has resulted in improved sensorimotor, but not cognitive function after TBI (210). Lu et al. (211) found that human umbilical cord blood cells injected i.v. into traumatic brain injured rats significantly reduced motor and neurological deficits compared with control groups by day 28 after the treatment. The cells were observed to preferentially enter the brain and migrate into the parenchyma and express the neuronal markers, NeuN and MAP-2, and the astrocytic marker, GFAP. These data suggest that the transplantation of progenitor cells into the brain may be a potential therapy for patients who have sustained traumatic brain injuries

### NUTRACEUTICALS

Several empirical research studies have demonstrated that “natural” treatments can be effective in reducing some of the sequelae of TBI. An excellent example of a nutraceutical that has been extensively reported to reduce

secondary effects of TBI and improve behavioral outcome is magnesium ( $Mg^{2+}$ ). Early work has shown that the administration of  $Mg^{2+}$  30 min after a fluid percussion injury in rats provides significant improvement in neurological function when compared to saline-treated rats (212). Follow-up studies from the same group have shown that  $Mg^{2+}$  therapy is also effective in decreasing cognitive and motor deficits (58,213), histological damage (214,215), and expression of a gene (p53) associated with the induction of cell death (216). The beneficial effects of  $Mg^{2+}$  have been observed for up to 8-mo after TBI (217). Using an impact-acceleration model of severe traumatic diffuse axonal brain injury, Heath and Vink (218) have shown that intramuscular administration of  $MgSO_4$  (750  $\mu$ mol/kg) at 30 min or at 8, 12, or 24 hr after TBI significantly improves motor performance as assessed on a rotarod test vs. untreated-control animals. Although the rats treated at 24 hr displayed a slower rate of recovery during the early testing period, they eventually recovered significantly beyond the vehicle-treated group by the end of the testing session, suggesting that even delayed magnesium treatment is effective after TBI (218). A more recent finding by the same group reports that  $MgSO_4$  (250  $\mu$ mol/kg) at 30 min after diffuse TBI significantly improves sensorimotor function and learning performance (219).  $Mg^{2+}$  therapy has also been shown to facilitate functional recovery and prevent subcortical atrophy after lesions of the rat sensorimotor cortex (220).

Other nutraceuticals that have been reported to positively impact the neuroprotective and/or rehabilitative process after TBI include, but are not limited to, cytidinediphosphocholine (CDP-choline), creatine, and vitamins B3 and E. CDP-choline or citicholine is a naturally occurring endogenous nucleoside and an intermediate of phosphatidylcholine synthesis. When administered as a treatment after controlled cortical impact injury (100 mg/kg, 1–18 days post-TBI), CDP-choline-treated rats performed significantly better than vehicle-treated rats on both motor and cognitive tasks (176). Also utilizing the controlled cortical impact injury model, Baskaya et al. (221) demonstrated that intraperitoneal injections of CDP-choline (100 or 400 mg/kg twice after TBI) significantly decreased brain edema and BBB breakdown. In a more recent study, Dempsey and colleague reported that two treatments of CDP-choline (200 or 400 mg/kg, immediately post-TBI and 6 hr later) after cortical impact injury significantly prevented hippocampal neuron loss, decreased cortical contusion volume, and improved neurological recovery (222). Taken together, these studies indicate that CDP-choline is an effective neuroprotective agent on secondary injuries and neurobehavioral dysfunctions that are manifested after TBI. Creatine, a common food supplement used by individuals as a performance enhancer, has been demonstrated to attenuate the extent of cortical damage in mice and rats by as much as 36 percent and 50 percent,

respectively (223). The authors suggested that protection might have been mediated by mechanisms involving creatine-induced maintenance of mitochondrial membrane potential, decreased intramitochondrial levels of reactive oxygen species and calcium, and preservation of adenosine triphosphate levels. In a study investigating the effects of vitamin B3, Hoane et al. (224) reported that a 500 mg/kg dose provided 15 min and 24 hr after TBI produced by a cortical contusion model significantly reduced the size of the lesion and glial fibrillary acidic protein positive astrocytes compared to saline-treated rats. Furthermore, vitamin B3 treatment also significantly improved behavioral outcome (224). The data suggest that vitamin B3 may have therapeutic potential for the treatment of TBI. In an investigation of vitamin E or  $\alpha$ -tocopherol, Inci and colleagues have demonstrated that this nutraceutical also exhibits protective effects after TBI. Specifically, guinea pigs were subjected to a TBI utilizing a weight drop injury model and then administered 100 mg/kg of vitamin E. Lipid peroxidation was measured using the thiobarbituric acid reactive substances method immediately, 1 hour, or 36 hr after trauma. The results indicated that  $\alpha$ -tocopherol significantly suppressed the rise in lipid peroxide levels in traumatized brain tissue, suggesting that this treatment regimen has a protective effect against oxygen free radical-mediated lipid peroxidation after TBI (225).

## CONCLUSIONS

The experimental control afforded with the utilization of animal models of TBI has allowed for the testing of several classes of neuroprotective therapies. Empirical studies have revealed several potential treatments that attenuate a range of neurobehavioral and morphological derangements. However, the translation of experimental neuroprotective treatments to humans has been limited. This situation may be improved by screening therapies under experimental conditions that better reproduce the clinical environment (e.g., ICU-like care, large animal models, etc.), and by conducting clinical trials that better mimic laboratory treatment administration protocols (e.g., earlier treatment windows).

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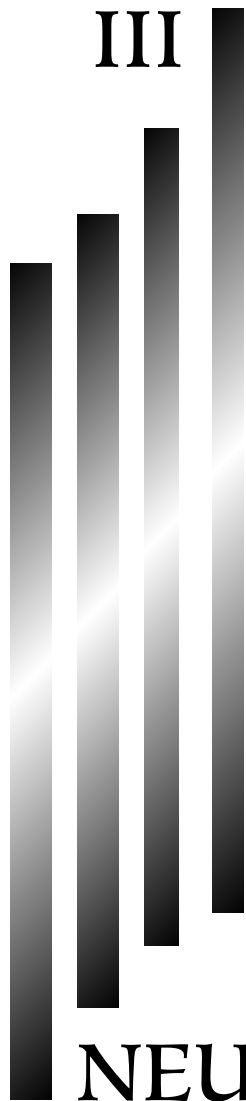
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**NEUROIMAGING AND  
NEURODIAGNOSTIC  
TESTING**



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# 11

## Static Neuroimaging in the Evaluation of TBI

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### INTRODUCTION

Traumatic brain injury is a common problem in emergency facilities—especially in urban trauma centers. Surgical and medical management depend on the specific injuries a patient has sustained and a timely diagnosis at the time he or she enters the emergency center. Surgical and medical management also depends on both clinical data and imaging results. Both are essential for the appropriate selection of therapy.

Medical imaging has progressed substantially in the last several years, in part due to advances in neurological imaging. Imaging is a representation of the underlying vital structures that are deep below the skin. The human brain is a three-dimensional entity, but it is converted by hardware, software, and digital technology into a two-dimensional image that can be viewed on a sheet of film or at a computer workstation. One of the principal reasons that the field of radiology has advanced so much in the last several years has been the computer industry. The ability to digitally display and store high-resolution images has improved substantially.

Plain film radiography provides very little useful information for patients with traumatic brain injury (1). Plain films may be used to look for foreign bodies or visualize fractures, however computed tomography (CT) and magnetic resonance imaging (MRI) are essential for the

accurate diagnosis and subsequent management of patients with traumatic brain injury. While MRI has made remarkable advances in the past 10 years, CT continues to be the initial imaging modality for the brain in the acute setting (2). Three-dimensional reconstructions of axial CT data may now be obtained, essentially eliminating plain film radiography from the imaging arsenal used in the work-up of acute trauma.

One should understand the pathophysiology of different brain injuries and recognize these injuries in any form of imaging. While technology does change, the pathophysiology and appearance of these lesions remains the same. It is our hope that by the end of this chapter, the reader will have formed a sound understanding of the imaging appearance of the major pathologic entities of traumatic brain injury encountered in clinical practice. Both CT and MRI are described separately below, followed by the specific traumatic entities that are organized in a systematic fashion.

### IMAGING TECHNIQUE

Modern digital imaging technology allows manipulation of data to reconstruct images in multiple planes. This manipulation of data allows the interpreting physician to gain three-dimensional information about the human

brain from two-dimensional data. In addition, there are currently many three-dimensional techniques available for certain applications, although not practical in the acute setting. Imaging of the traumatically injured brain should be fast, reliable, diagnostic, and widely available. The workhorse of any facility continues to be CT scanning. Helical CT is extremely fast. It allows the technician to obtain whole-body images in a single breath hold. This is of paramount importance in patients who have sustained polytrauma of other organs in addition to brain injuries.

Many investigators have attempted to develop criteria for obtaining a CT scan in the acute setting for the evaluation of traumatic brain injury. The American College of Radiology (ACR) conducted a study in 1986 that ultimately divided neurologically traumatized patients into three groups of risk: low, moderate, and high. The low-risk group consisted of patients with minor symptoms without neurological deficits such as headache, dizziness, or scalp injuries. It was proposed that this group of patients could be observed without the need for imaging. The moderate- and high-risk groups included those patients with neurological deficits, altered consciousness, seizures, depressed skull fractures, or penetrating injuries. It was proposed that these patients should receive a non-contrast CT scan of the brain as part of the initial work-up (3). Although the ACR and others have attempted to define the indications for obtaining an imaging study in minor trauma, currently this is a multifactorial decision made in emergency centers across the country. Some researchers have also found that brain injuries detectable by CT imaging may occur in people with relatively minor complaints, normal neurological exam and/or a normal Glasgow Coma Scale (GCS) of 15 (4). Issues such as cost, risk-to-benefit ratio, and medical/legal concerns play roles in the decision to image patients with mild brain injuries or post-concussive disorders.

### Computed Tomography

Sir Godfrey N. Hounsfield of Great Britain and Allan M. Cormack of the United States won the 1979 Nobel Prize in Medicine for their groundbreaking work that made CT a reality in the 1970s. A conventional CT scanner consists of a gantry, table, and computer workstation. Early CT scanners were slow and cumbersome. Only one slice could be acquired at a time. The incorporation of slipping technology in the 1990s allowed helical CT units with a continually rotating gantry to become available. With helical CT, the table and the patient are continually moving through the gantry. Many of these units also employ multiple detector arrays that increase the volume of tissue imaged and improve the speed with which the study is performed. Current multiple detector helical CT scanners produce remarkable images and allow versatile

reconstruction of volume data in multiple planes—axial, sagittal, coronal, and oblique projections. These units are four to six times faster than older helical units. An entire CT of the abdomen and pelvis may be performed in a trauma patient with a single breath hold in less than 30 sec. CT scans of the brain may be performed even faster.

The raw data obtained from CT detectors is mathematically manipulated using several algorithms and filters to obtain visual data that offers both spatial and contrast information. The visual contrast between different tissues when viewing a CT image is due to differences in the absorption of x-rays. The properties that govern x-ray absorption on plain films are identical for CT. As x-ray photons pass through air and tissue, the useful beam is subject to attenuation—or removal of photons (5). The x-rays may be attenuated (absorbed), scattered in a new direction, or pass through the tissue of interest.

The two extremes of air and metal have characteristic appearances on CT because no x-rays are absorbed by air while nearly all x-rays are absorbed by metal. Everything in between these two extremes has a spectrum of CT appearances. Visually, air is black, fat is dark, and soft tissue and fluid are shades of gray. Bone is white and metal is extremely bright—often causing streak artifact on the CT images. The Hounsfield Scale, named for the father of computed tomography, allows one to quantitate the actual tomographic densities of these different tissues. In fact, CT's ability to distinguish between subtle differences of similar tissues—or contrast resolution, is the true advantage of CT as an imaging modality. Hounsfield Units (HU) are numerical values that are assigned to each pixel (picture element) in a CT image. The scale is roughly  $-1000$  to  $+3000$ . Water or simple fluid like cerebrospinal fluid (CSF) is set as the baseline of zero. Air is black, or  $-1000$ , while bright metal or iodinated contrast material is close to  $+3000$ . Soft tissue ranges from about  $-200$  to  $+200$ . Gray matter of the brain is typically around  $30-40$  Hounsfield units. When interpreting a CT image of the brain, the density of surrounding structures or abnormalities is often compared to gray matter. A typical radiology report may read, "there is an intra-axial mass that is isodense (the same density) to gray matter."

Another advantage of CT is the ability to manipulate the raw data to augment certain visual characteristics for the person interpreting the image. Bone windows, brain windows, soft tissue windows, lung windows, and so on, are simply different ways of viewing the same raw data to take advantage of contrast differences. These different window settings are made by employing unique computer algorithms, or filters, to manipulate the raw data. These settings have both a window level and a window width. A window level is the center value of a certain setting, while the window width is the range around the center value. It is the window width that determines

the visual contrast or “shades of gray” displayed for a certain setting (5). The window level accounts for the tissue brightness that is displayed (6).

The only absolute contraindication to obtaining a non-contrast CT is an unstable patient. Because CT imaging uses ionizing radiation, special care should be used with children and pregnant patients. Organs that are not included in the region of interest may be shielded with lead to protect them from unnecessary exposure to radiation. Although there is no danger with obtaining CT in patients with aneurysm clips or intracranial metal, these objects do create artifacts that render the interpretation of a CT difficult.

In order to perform a CT, the patient is placed in the supine position on the table and moved into the gantry. A CT scout image, or topogram, is obtained in order to determine the area that should be scanned. The scout image looks like a lateral plain film of the skull. The technologist can then orient the plane of the scan and set the slice thickness. Typically, the axial images are obtained parallel to the orbital roof. A trauma CT scan of the brain is performed without contrast in order to identify acute hemorrhage, which appears hyperdense (bright) on CT.

CT may also be obtained after the administration of intravenous, iodinated contrast material. Contrast is usually not needed in the evaluation of acute traumatic brain injury, unless screening of the vasculature is warranted. For suspected vascular injury, dedicated conventional angiography is often performed rather than CT angiography because of increased sensitivity and the ability for therapeutic intervention to be performed quickly if needed. Thus, routinely giving contrast for a CT in the acute setting for a patient with suspected brain injuries is a wasted step and may obscure underlying acute hemorrhage.

Contrast is administered in order to evaluate medical pathology for which the blood-brain barrier has been violated. These include inflammatory, infectious, vascular, and neoplastic abnormalities. Contrast is given to identify the enhancement patterns of intracranial mass, cerebral abscess, subdural empyema, encephalitis, and vasculitis. Contrast material is also required for performing CT angiography in order to visualize the enhancing arteries and veins.

With the advent of multidetector CT (MDCT), fast imaging of large volumes of tissue is possible, without sacrificing spatial resolution. MDCT with thin slices can be combined with software packages that optimize vascular enhancement. This allows one to control the intravenous bolus of contrast, specifying arterial phase and delayed venous phase scanning. This becomes important for CT angiography and evaluation of intracranial vasculature noninvasively. Post-processing techniques such as maximum intensity projection (MIP), volume rendering (VR), shaded surface display (SSD), and curved planar reformatted images allow one to manipulate the MDCT data to optimally display intracranial vascular

structures and detect pathology such as arterial occlusion, dissection, pseudoaneurysm formation, and vasospasm. Goldsher et al. evaluated 36 patients presenting with subarachnoid hemorrhage using MDCT angiography of the vertebrobasilar system. Their results suggest that cerebral MDCT angiography is a reliable, rapid, and minimally invasive diagnostic method, for assessing vasospasm of the posterior circulation in patients with subarachnoid hemorrhage (7). More studies are needed at large volume trauma centers to further define the role of MDCT angiography in the evaluation of traumatic intracranial vascular injury.

Sequential axial nonenhanced images of the brain are performed from the base of the skull through the vertex with slices that vary in thickness from 5 mm to 7 mm. Current helical scanners obtain overlapping voxels (volume elements) of tissue continuously from start to finish. The raw CT data is manipulated and sent to a workstation for processing. Images may then be viewed in different window settings on the workstation, film or Picture Archiving and Communication System (PACS). CT scans of the brain are often viewed in bone windows (window level: 700, window width: 3500), brain windows (window level: 40, window width: 100) and intermediate windows (window level: 80, window width 250)—for purposes of identifying subtle hemorrhages along the surface of the brain (1). Many hospitals are now converting to digital PACS systems in order to take advantage of the ability to manipulate data, eliminate film costs and allow clinicians to access a computer version of images and reports.

### Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is an imaging technique that plays an adjunctive role in brain injury. The ability for tissue/fluid characterization and multiplanar imaging are advantages of MRI. While the imaging times of MRI have shortened with improved equipment and stronger magnets, performing an MRI is still much longer than performing a CT scan. Thus, the use of MRI in patients with acute traumatic brain injury is limited to certain patient populations. When compared to CT, MRI provides exquisite soft tissue detail, evaluation of the brainstem, skull base, and cranial nerves. It displays particularly well the posterior fossa, which is often obscured by a beam-hardening artifact that occurs with CT.

MRI is used primarily in the work-up of chronic conditions or for following the sequelae of traumatic brain injury. It is more accurate in assessing the general age of intracranial blood products. The appearance of evolving intracranial hemorrhage is described in detail later in the text. MR angiography is a technique that is useful to screen for concurrent vascular injuries in the head and neck. However, conventional angiography

remains the gold standard in the evaluation of traumatic vascular injury, both for diagnosis and the opportunity for endovascular therapy such as embolization, angioplasty or stenting.

The human body is made up of water, natural elements, minerals and macromolecules such as proteins, fats, and carbohydrates. One of the main components is the hydrogen proton. Magnetic resonance imaging relies on the signal emitted by relaxing protons as they are disturbed by external magnetic fields and radiofrequency pulses. An MRI unit consists of a powerful external magnetic field, transmitting coils, receiving coils, patient table and a digital workstation (Figure 11-1). With the application of a strong external magnetic field, hydrogen protons in the body align themselves either parallel or anti-parallel with this field. Most of the protons align themselves with the lower energy parallel state, creating a net magnetic moment in the direction of the external magnetic field (8). This net magnetic moment in the direction of the external magnetic field is called the longitudinal vector.

Each proton has a spin and a motion called precession. The frequency with which the protons precess depend on the strength of the external magnetic field. The relationship between the precession frequency and the external magnetic field is described by the Larmor equation (5, 8):

$$\omega_0 = \gamma B_0$$

$\omega_0$  is the precession frequency (Hz)

$\gamma$  is the gyro magnetic ratio

$B_0$  is the strength of the external magnetic field (Tesla)

It can be derived from the equation that the precession of protons varies directly with the strength of the magnetic field. Stronger magnets produce faster precession.



FIGURE 11-1

Standard 1.5 Tesla MRI gantry

This property allows for a higher signal and improved image quality. Most diagnostic quality magnets available in hospitals or outpatient facilities are in the 1.0–1.5 Tesla range. Magnets in the 3.0–7.0 Tesla range are now being used in academic centers for human and animal research. Stronger magnets will improve the quality, signal-to-noise ratio, and speed of acquisition of MR images in the future.

A radiofrequency pulse (RF) at the same frequency as the precessing protons is then turned on. This pulse disrupts the parallel/antiparallel equilibrium of the protons within the external magnetic field. Some protons are flipped into the higher-energy state, or antiparallel orientation. This eliminates the net magnetic longitudinal vector that had been in the direction of the external magnetic field. This disruption of the longitudinal vector, or transfer of energy from the RF pulse to the precessing protons is called *resonance* (8). The RF pulse results in a decrease or elimination of the longitudinal net magnetization and also allows the protons to precess in phase with one another. Because the protons are precessing in phase during the RF pulse, a net magnetization in the transverse direction is then created. Thus, after the RF pulse is turned on, the longitudinal magnetization in the direction of external magnetic field decreases, while a new transverse magnetization is created due to the protons now precessing in phase.

The RF pulse is then turned off. Protons gradually flip back to the lower-energy parallel orientation in the direction of the external magnetic field. The longitudinal magnetization vector gradually reappears. The reappearance of the longitudinal vector is called longitudinal relaxation and is described by the time constant  $T_1$ , or longitudinal relaxation time. The transverse magnetization that had been created by the protons precessing in phase disappears when the RF pulse is turned off. This is described by the transverse relaxation time,  $T_2$ .  $T_1$  relaxation depends on the strength of the external magnetic field, tissue composition and structure.  $T_2$  relaxation is affected by magnetic field inhomogeneities.

Each type of tissue has unique  $T_1$  and  $T_2$  properties that affect how they will appear on an MR image. When the RF pulse is turned off, special coils around the patient detect the signal of the increasing longitudinal vector and decreasing transverse vector (8). The decay and growth of these relaxation properties may be plotted on a graph. By changing different parameters and imaging times of the MRI sequence, one can take advantage of the different points along these relaxation curves, thereby affecting the signal of different tissues. These parameters can render an image  $T_1$  weighted,  $T_2$  weighted, or a combination of the two. In addition, each tissue has a certain proportion of protons per unit volume. Parameters can also be changed to take advantage of this proton density. For instance, water or fluid has a long  $T_1$  and is typically dark on a  $T_1$  weighted image and bright on a  $T_2$  weighted

image. Fat has a short  $T_1$  and is typically bright on both  $T_1$  and  $T_2$  weighted images.

In order to localize the protons or the signal created within tissue, gradient magnetic fields are applied in a multiplanar fashion. The applied external magnetic field created by the MR gantry is fairly uniform or homogeneous. Gradients are applied to the main magnetic field to create local differences across the area of interest. In other words, the magnetic field will change across the patient in several directions, determined by the gradients applied. These magnetic field gradients are imposed on the external field in order to change the precession frequency of each proton in the body slightly, allowing spatial localization to take place. Each proton can be identified in space and location because of its unique spin created by applying these known gradient fields across the regions of interest. The magnetic field gradients and radiofrequency excitations help to localize the signal from each voxel (volume element) within the patient being imaged (5, 8). It is beyond the scope of this chapter to describe the specific appearance of each tissue within a myriad of MR pulse sequences that seem to change daily.

CT is the dominant imaging modality for the detection of traumatic brain injury in the acute setting, while MRI is very helpful for the detection of occult lesions, follow-up and the long-term management of patients with traumatic brain injuries. Most initial decisions concerning management, such as surgery or no surgery in the emergency setting, are made based on the findings of a non-contrast CT of the brain. MRI may be obtained in the acute setting if there are clinical findings out of proportion to the CT findings, suggesting diffuse axonal injury or stroke. MRI also shows the chronic sequelae of the initial injury with excellent detail. Some common indications for obtaining an MRI in a post-traumatic work-up include chronic headaches, stroke, pseudoaneurysm, dementia, hydrocephalus, cranial nerve palsy, cavernous sinus injuries, persistent neurological deficits, or patients with diffuse axonal injury in light of a normal CT of the brain (1, 9, 10). The findings on MRI have implications on predicting patient outcome as well, and this topic will be discussed at the end of the chapter.

Gadolinium is a rare earth element with an atomic number of 64 that can be chelated to form MRI contrast material. Intravenous gadolinium chelate is non-iodinated and contrast reactions or renal failure are much less common than with iodinated contrast material. Gadolinium is paramagnetic, meaning that it affects the  $T_1$  and  $T_2$  characteristics in such a way that enhancement on post-contrast  $T_1$  images can be seen. Gadolinium provides the same information that iodinated contrast provides on CT—it allows visualization of vasculature and areas of breakdown of the blood-brain barrier. MRI is often used in the subacute or chronic setting of relatively stable patients. Gadolinium is extremely safe and it is often used

in many protocols after noncontrast MR images have been obtained.

## BRAIN INJURY

Imaging technology changes quickly; thus it is advantageous to learn pathology in an organ-based fashion. No matter how the technology changes, the pathology remains the same. With the basic knowledge of pathophysiology, one can learn and adapt to how a particular condition appears within a myriad of changing imaging modalities. Imaging of patients with traumatic brain injury in the acute setting often begins with a noncontrast CT of the brain (6). All of the available data including history, physical exam, mechanism of injury, and vital signs are used in conjunction with the imaging evaluation to triage these patients into surgical or medical management. If surgery will be needed, decisions as to the timing of surgery are also made based on the clinical presentation and imaging results. These acute injuries may require early neurosurgical intervention and a timely interpretation of the imaging findings is advantageous in the emergency room setting (11).

When interpreting an emergent CT scan of the brain, particular attention should be paid to the midline structures, presence of shift, ventricles, basal cisterns, the presence of herniation, cerebral convexities, and mass effect (12). The skull of infants and young children has open sutures and fontanelles; thus there is more plasticity of the cranial vault, should pathology develop. The adult brain exists in a closed box, the densely ossified skull that does not yield to intracranial pathology. Skull fractures, particularly depressed fractures often herald underlying brain injuries. Another advantage of CT is the exquisite bony detail it offers. Subtle, nondisplaced fractures in the plane of the scan may go undetected; however, these are felt by many researchers to be clinically insignificant (3,13). CT allows one to characterize fractures, the extent of bony injury and the sequelae of these fractures to the underlying brain parenchyma.

Air present within the skull or brain is termed pneumocephalus. The presence of pneumocephalus often heralds the presence of a fracture, usually communicating with air in the sinuses or outside of the skull. It is imperative to recognize fractures involving neurologically exquisite areas such as the orbit or the temporal bone. Temporal bone fractures, depending on type may lead to cerebrospinal fluid otorrhea, conductive hearing loss, sensorineural hearing loss or facial nerve paralysis. Other fractures such as nondisplaced calvareal fractures may be managed conservatively.

There is a finite amount of space within the adult skull. If something occurs within the skull to occupy the space, it occurs at the expense of the brain that is soft and

very pliable. In response to a space-occupying intracranial lesion, the brain may become deformed, swollen or edematous. If the mass effect within the skull is severe enough, a herniation syndrome may result. The brain is made up of gray and white matter. The gray matter consists of the cerebral cortex, cerebellar cortex, and deep nuclei. The white matter consists of a network of axons—connections and tracts between these nuclei. Injuries involving the brain itself—the gray or white matter of the brain parenchyma, are called intra-axial injuries. The extra-axial space, on the other hand, is outside of the brain parenchyma. The brain is separated from the inner table of the calvarium by several layers of tissue called meninges.

The meninges are composed of different layers of connective tissue. The dura is the outer layer that is firmly attached to the inner table and periosteum of the skull. The arachnoid exists between the dura and the pia. The pia is a thin lining that covers the brain and spinal cord. It follows the cortex of the brain and lines each gyrus, while dipping into the intervening sulci. The subarachnoid space is the space bounded by the arachnoid layer and pia. It contains cerebrospinal fluid and blood vessels. There are several areas within the brain where the subarachnoid space expands to create cisterns. Abnormalities that affect the subarachnoid space may extend into these cisterns (14). The pia and arachnoid comprise the leptomeninges. Injuries outside of the brain parenchyma are called extra-axial injuries.

The brain and spinal cord are bathed in cerebrospinal fluid (CSF). This fluid is also present in the ventricles and cisterns of the brain. There are two lateral ventricles, with frontal, temporal, and occipital horns. The third and fourth ventricles are unpaired, midline structures. The lateral ventricles communicate with the third ventricle through the paired foramina of Monro. The third ventricle communicates with the fourth ventricle—which is in the posterior fossa of the brain through the cerebral aqueduct. In the normal state, the CSF volume remains relatively constant, although it is constantly in flux. A homeostasis is reached where the amount of CSF produced in the choroids plexus is the same as the amount of CSF being absorbed into the venous sinuses. Cerebral capillaries form an impermeable blood-brain barrier and the capillaries and ependymal cells form a blood-CSF barrier (14). These barriers may break down in pathological conditions such as trauma, infection or tumor. Injuries within the ventricles or CSF spaces, while inside the confines of the brain, are actually outside the brain parenchyma and thus are extra-axial injuries. Sometimes, it is difficult to determine whether a lesion is intra-axial or extra-axial, however there are signs on imaging that help to define the location of lesions.

In the sections that follow, several types of traumatic brain injury will be discussed. The injuries are organized

according to location. Injuries involving the brain parenchyma, or intra-axial space will be discussed first, followed by a discussion of extra-axial manifestations of traumatic brain injury.

### Intra-axial: Brain Contusions

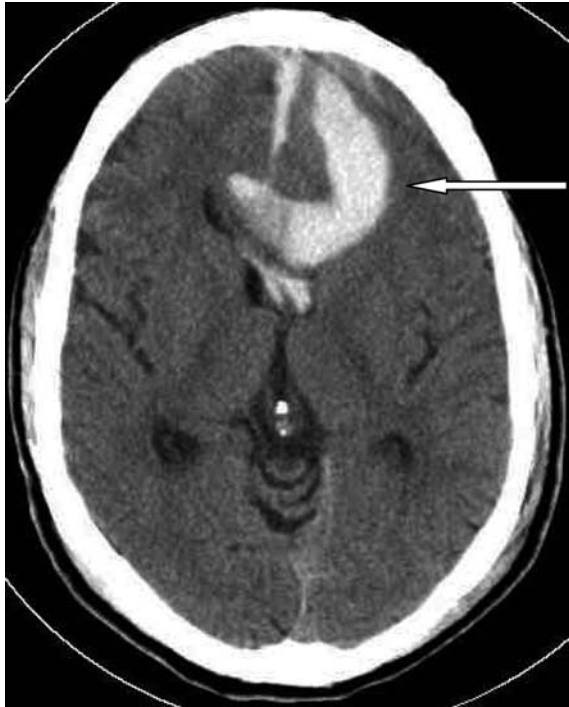
Some authors have described brain injuries based on the mechanism of injury—such as impact injuries versus inertial injuries, or primary versus secondary injuries (15). The traumatic neuropathology described in this chapter will be divided into intra-axial injuries and extra-axial injuries. Injury of the brain may occur from blunt or penetrating forces. Lesions such as brain contusions or epidural hematomas occur due to direct force, while other injuries, described later, occur due to acceleration/deceleration or rotational forces.

Direct forces may impact on the skull and underlying brain to cause injury to the brain parenchyma. These manifest acutely as brain contusions (Figure 11-2). A contusion may be hemorrhagic (Figure 11-3) or nonhemorrhagic, and all involve the gray matter of the brain. The two main reasons for not giving contrast prior to imaging a patient with acute intracranial injuries are to perform the exam quickly and to look for intracranial blood products.



FIGURE 11-2

Intra-axial hematomas: Axial noncontrast CT demonstrates intra-axial contusions in the bilateral frontal lobes and left temporal lobe (arrows). There is associated vasogenic edema



**FIGURE 11-3**

Hemorrhagic contusion: Axial noncontrast CT demonstrates a hemorrhagic contusion (arrow) in the left frontal lobe that extends across the midline and is associated with left to right shift and subfalcine herniation

Acute blood within the brain is bright on a non-contrast CT of the head, as is contrast material. Thus, contrast is withheld when evaluating the brain. The brightness of blood occurs due to the globin moiety of hemoglobin. Dehydration or an increase in hematocrit, may lead to a dense appearance of normal intracranial vasculature. In addition, hemorrhage may also appear denser than expected in these conditions (16).

Everything bright in the brain on CT may not always be due to acute hemorrhage. Calcification is also bright, and presents physiologically in the pineal gland and choroid plexus. In addition, the basal ganglia may exhibit calcification that is usually symmetrical from side to side. Dystrophic calcifications sometimes occur within the brain parenchyma due to prior infection or trauma. These dystrophic calcifications do not have mass effect or edema associated with them and will not enhance. Hemorrhagic contusions typically have a hypodense (dark) rim around them that represents edema (6). Arterial and venous malformations may also appear bright on CT, but are non-traumatic in nature. These conditions are associated with avid, tubular enhancement. In the case of an arterial-venous malformation, one may detect a nidus of tangled vessels that are associated with a prominent draining vein. These congenital or acquired vascular malformations are occasionally mistaken for traumatic injuries to the

untrained eye. Follow-up imaging such as MRI or angiography are obtained to further characterize these lesions as vascular malformations.

Hypodense lesions on CT (dark lesions) usually indicate the presence of ischemia, infarction or contusions that are non-hemorrhagic (17). While bright contusions are hemorrhagic, non-hemorrhagic contusions are hypodense—or darker than the surrounding brain on noncontrast CT images. This is due to local edema and fluid. Small lesions are often nonhemorrhagic or the blood is beyond the resolution of CT and not visible on the image. These types of lesions may be missed on CT. Other dark, nontraumatic lesions such as lipomas, dermoids, or arachnoid cysts can be characterized as such due to the presence of fat or fluid density.

By definition, all brain contusions are intra-axial and involve the brain parenchyma. Specifically, they involve the gray matter of the brain cortex and typically occur in the anterior and basal aspects of the frontal, temporal, and occipital lobes. These regions are most susceptible to contusions because of the bony ridges immediately adjacent to the aforementioned locations. Temporal lobe injuries are adjacent to the petrous bone or greater wing of the sphenoid bone. Frontal lobe contusions are adjacent to the cribriform plate or lesser wing of the sphenoid bone (12). Contusions occur in 5–10 percent of patients with moderate or severe head trauma (18). They cause local mass effect of surrounding structures and efface adjacent sulci, ventricles and cisterns. When at the brain periphery, they form acute angles with the skull. If the contusion is located immediately adjacent to the site of external trauma, it is a coup injury. If the contusion is opposite to the site of external trauma, it is a contra-coup injury. If the contusions are large enough, they may cause severe mass effect, midline shift or herniation. These large contusions may require neurosurgical intervention to prevent secondary injuries to the remaining brain such as infarction due to vascular compression, hydrocephalus or cranial nerve palsy. Hemorrhages of the deep gray matter nuclei such as the basal ganglia sometimes occurs after severe mechanisms of injury due to rupture of perforating vessels.

In contrast to the CT appearance of hemorrhage—which depends upon the globin moiety of hemoglobin—the MRI appearance of hemorrhage is quite variable. MRI provides much more detailed information, regarding the chronicity of blood products. This is due to the ability of MRI to characterize, in a temporal fashion, the process of blood product degradation. The MRI imaging parameters, the timing of the hemorrhage and the oxidation of iron in hemoglobin all affect the appearance of blood products on MRI. Acute hemorrhage contains oxygenated hemoglobin, or oxyhemoglobin inside red blood cells. Acute blood within minutes after bleeding is composed of oxyhemoglobin appears similar to fluid (low T1, high T2).



Oxyhemoglobin is isointense (similar) to gray matter on T1-weighting, and hyperintense (bright) relative to gray matter on T2-weighting. Oxyhemoglobin is rarely detected with MRI unless the patient is actively bleeding or is sustaining intermittent bleeds prior to the MRI. Active bleeding is rarely appreciated on MRI because the exam is obtained in a delayed fashion, after the patient is stable. This is in contrast to CT, where patients are often imaged in the acute setting, and often require emergent therapy while in the gantry. Many of the treatment decisions prior to obtaining an MRI have already been made from the findings seen on noncontrast CT.

Within hours after acute intracranial hemorrhage, blood within the red blood cells becomes deoxygenated (8–72 hr), resulting in conversion from oxyhemoglobin to deoxyhemoglobin. This appears hypointense (dark) on both T1- and T2-weighting. During this phase, hemorrhage may be difficult to detect or qualify based on routine MRI parameters. Gradient echo sequences are often helpful in these instances, because of the magnetic susceptibility artifact caused by the iron moiety in hemoglobin (19). Magnetic susceptibility occurs due to drastic changes in tissue magnetization at tissue/air or tissue/metal interfaces (5). This entity causes a blooming appearance, or an enlarged hypointense (dark) halo around areas of metal, hemosiderin or air. The iron that becomes deposited within areas of hemorrhage is often detectable months after the injury on gradient echo MRI, when other MRI sequences have normalized (20).

After 3 to 7 days, intracellular deoxyhemoglobin becomes oxidized into intracellular methemoglobin, that appears hyperintense (bright) on T1-weighting and hypointense (dark) on T2-weighting. After 10 to 14 days, the red blood cells are broken down, releasing extracellular methemoglobin—that is, a paramagnetic substance and appears bright on both T1- and T2-weighting. Other substances that are bright on a T1 weighted image include gadolinium, fat, melanin and proteinaceous substances. Blood products are classically described as one of the causes of hyperintense (bright) foci on a precontrast T1-weighted MRI image. As stated earlier, because an MRI is usually obtained well after the acute insult, blood products are usually in the methemoglobin phase, which is bright on T1.

As white blood cells are mobilized to the site of chronic blood (months to years after hemorrhage), the extracellular methemoglobin is stored as ferritin and hemosiderin. Ferritin and hemosiderin appear hypointense (dark) to gray matter on both T1- and T2-weighting (1, 21–23). This appears as a dark ring—the hemosiderin ring around areas of old hemorrhage. Gradient echo and susceptibility sequences, as mentioned previously are exquisitely sensitive to iron or metal. This allows the sequelae of prior hemorrhage to be detected months to years after the inciting injury. In addition, these sequences are good for detecting

blood products or hemosiderin within the sulci and subarachnoid spaces—leptomeningeal hemosiderosis. Leptomeningeal hemosiderosis involves deposits of hemosiderin (iron) within the sulci, causing diffuse low signal intensity within sulci on T1 and T2 weighting.

In summary, the appearance of blood products on MRI is quite variable and depends on the timing of imaging in relation to when the injury occurred. The ability of MRI to image the physiologic degradation and evolution of hemorrhage allows one to more accurately describe the age of blood products. To review, hemorrhage evolves from hyperacute oxyhemoglobin (high T2) to acute deoxyhemoglobin (low T1, low T2) to early subacute intracellular methemoglobin (high T1, low T2) to late subacute extracellular methemoglobin (high T1, high T2), and finally to chronic hemosiderin (low T1/T2 ring; magnetic susceptibility).

### **Intra-axial: Shearing Injuries**

Shearing injuries, like parenchymal contusions, may be either hemorrhagic or nonhemorrhagic. They typically occur at the gray/white matter junction, in a subcortical location. These injuries result from acceleration or deceleration of the brain during trauma. Shearing injuries may also occur in the brainstem, corpus callosum and septum pellucidum (24). Like any small abnormality in the brain, subtle lesions may not be appreciated with CT. Occasionally, shearing injuries are manifested as 1–5 mm petechial areas of hemorrhage. MRI has the advantage of gradient echo and magnetic susceptibility sequences that take advantage of the blooming phenomenon that occurs in areas of hemorrhage on MRI. Thus, MRI may detect a greater number of small hemorrhages that may not be seen with non-contrast CT (25). Shearing injuries may manifest clinically as neurological, cognitive or behavioral impairment. Shearing injuries may also occur in infants and young children due to non-accidental trauma. Shaken baby syndrome classically produces shearing injuries within the brain as well as retinal hemorrhages (26). Shearing injuries may also result from the rotational forces and impact injuries that occur during certain types of athletic pursuits, most notably contact sports (27).

A normal CT scan in light of a neurologically devastated patient is a classic finding in diffuse axonal injury (DAI). It is the most common cause of a post-traumatic vegetative state (1). DAI consists of innumerable shearing injuries that are often beyond the resolution of CT (28). The injuries typically occur at the gray-white matter junction in the frontal and temporal lobes. In very severe trauma, diffuse axonal injury may occur in the lobar white matter, corpus callosum and brainstem (Figure 11-4). In the brainstem, these shearing injuries are typically located in the dorsolateral aspects of the pons and midbrain. DAI occurs after acute acceleration/deceleration forces disrupt

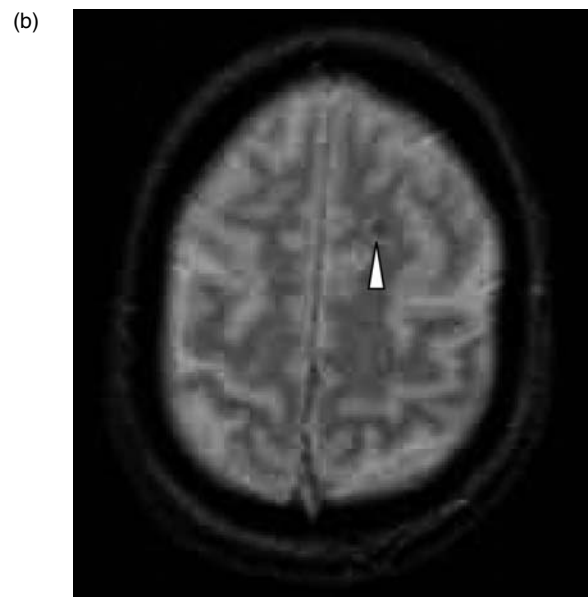
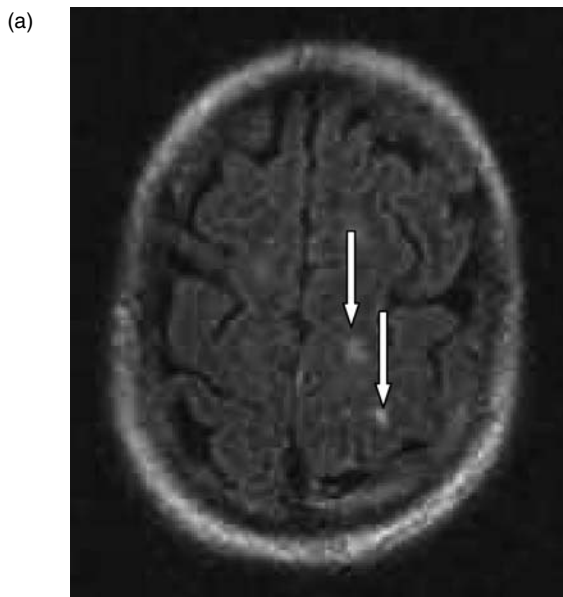


**FIGURE 11-4**

DAI: Axial noncontrast CT demonstrates shearing injuries involving the splenium of the corpus callosum and deep white matter (arrows)

neuronal axons. The mechanism of injury is typically severe such as that seen in high-speed motor vehicle accidents. If the axonal injuries are nonhemorrhagic, they will likely not be seen on CT. Because CT often misses these injuries, follow-up MRI in patients with DAI may demonstrate bright T2 foci at the gray-white interfaces or even delayed petechial hemorrhages (23). MRI is much more sensitive in the detection of diffuse axonal injuries than is CT (Figure 11-5). Many of these injuries likely go undetected on any imaging modality. Gradient echo MR sequences are sensitive for subtle blood products by taking advantage of the blooming, or magnetic susceptibility artifact that iron containing compounds produce, as previously discussed. Gradient Recalled Echo (GRE) and fluid-attenuated inversion recovery (FLAIR) MRI sequences are very sensitive for the subtle findings seen in patients with petechial hemorrhage and diffuse axonal injury (29).

As mentioned earlier, CT markedly underestimates the extent of these injuries. The CT appearance may be normal or near normal. Patients who have sustained diffuse axonal injury have a worse long-term prognosis than those patients with gray matter contusions, thus it is helpful to employ MRI for diagnosis in these situations. Contusions often occur due to direct impact injuries that occur in focal locations. Shearing injuries and DAI, on the other hand, occur from global rotational forces imparted to the brain. These types of forces result in more extensive and generalized injuries to the brain. MRI is also useful for imaging the long-term sequelae of patients with



**FIGURE 11-5**

DAI: Axial FLAIR MRI (a) demonstrates foci of increased signal intensity within the deep bifrontal and left parietal white matter (arrows). Axial gradient echo (b) demonstrates a focus of magnetic susceptibility in the left frontal white matter (arrowhead). These foci are typical of petechial hemorrhages seen in DAI

global brain injury. The long-term sequelae of DAI will be discussed in more detail at the end of the chapter.

### Intra-axial: Herniation Syndromes

Severe intracranial injuries such as large hematomas or brain swelling, exert mass effect on the pliable brain within the closed-box of the adult cranium. The production of CSF and cerebral blood flow vary inversely with increasing intracranial pressure. Intracranial pressure will change if there are additions or subtractions to the fixed intracranial contents (brain, CSF, blood). This is called the Monro–Kellie Doctrine (14). Mechanical displacement of the brain, if severe enough, may lead to herniation syndromes. These include subfalcine, transtentorial, tonsillar, transsphenoidal, or external herniation.

Subfalcine herniation consists of midline shift of the cingulate gyrus under the midline dural reflection of the falx cerebri. This results in effacement of the ipsilateral lateral ventricle and noncommunicating hydrocephalus of the contralateral lateral ventricle (23). Dilation of the contralateral ventricle in subfalcine herniation occurs because of obstruction at the level of the foramen of Monro. If severe enough, cerebral infarction in the anterior cerebral artery distribution may occur because of compression of the vessels under the falx cerebri. Subfalcine herniation is the most common herniation syndrome (30).

If the uncus portion of the temporal lobe herniates across the tentorium (Figure 11-6), the midbrain is compressed, leading to injury of the contralateral cerebral peduncle (Kernohan's notch) or ischemia/infarction in the posterior cerebral artery distribution. Uncal herniation may also cause an ipsilateral cranial nerve III (oculomotor nerve) palsy. Uncal herniation may manifest clinically as ipsilateral dilated pupil and an ipsilateral hemiparesis, the latter due to compression of the contralateral cerebral peduncle.

Transtentorial herniation occurs in a cranial or caudal direction across the tentorium, that separates the posterior fossa contents from the supratentorial compartment. Descending herniation through the tentorium appears on CT as effacement of the suprasellar and perimesencephalic cisterns. Transtentorial herniation may lead to disruption of brainstem perforating vessels, causing petechial hemorrhages in the midline brainstem, Duret hemorrhages. If the cerebellum herniates upward through the tentorium, the basilar cisterns are effaced. This typically occurs due to a posterior fossa hemorrhage or mass.

Cerebellar tonsillar herniation occurs when the inferior portion of the cerebellum herniates downward through the foramen magnum. Tonsillar herniation may cause infarction in the posterior inferior cerebellar artery territory (PICA). Cerebellar tonsillar herniation occurs due to a posterior fossa mass, hemorrhage or swelling. This is important to distinguish from nontraumatic



FIGURE 11-6

Uncal herniation: Axial noncontrast CT demonstrates a left-temporal subdural hematoma (arrow) associated with uncal herniation and compression of the midbrain (arrowhead). There is also contra-lateral dilatation of the temporal horn

cerebellar tonsillar herniation of greater than 5 mm through the foramen magnum—Chiari I malformation. Some of these patients with this congenital malformation are subject to trauma; however the herniation in these cases is not due to the trauma itself.

Transsphenoidal herniation occurs when the frontal or temporal lobes are displaced posteriorly or anteriorly across the greater wing of the sphenoid bone respectively. External herniation occurs when brain contents herniate through a bony defect—either fracture or surgical defect, outside of the calvarium. Any of the aforementioned herniation syndromes may occur due to mass effect from trauma, hemorrhage or neoplasm (12, 23). In some patients with severe mass effect, a combination of different herniation syndromes may result (Figure 11-7).

### Intra-axial: Cerebral Edema

The term *cerebral edema* is often misused or misunderstood. Global cell injury or cell swelling has been called cerebral edema in the past. Multiple injuries to the brain or anoxic insult may present as diffuse abnormality, or brain swelling. Brain swelling occurs because of increased cerebral blood volume, loss of autoregulation of cerebral blood flow, or a generalized increase in tissue fluid. This manifests clinically as elevated intracranial pressure. Radiologically, brain swelling manifests as diffuse effacement of



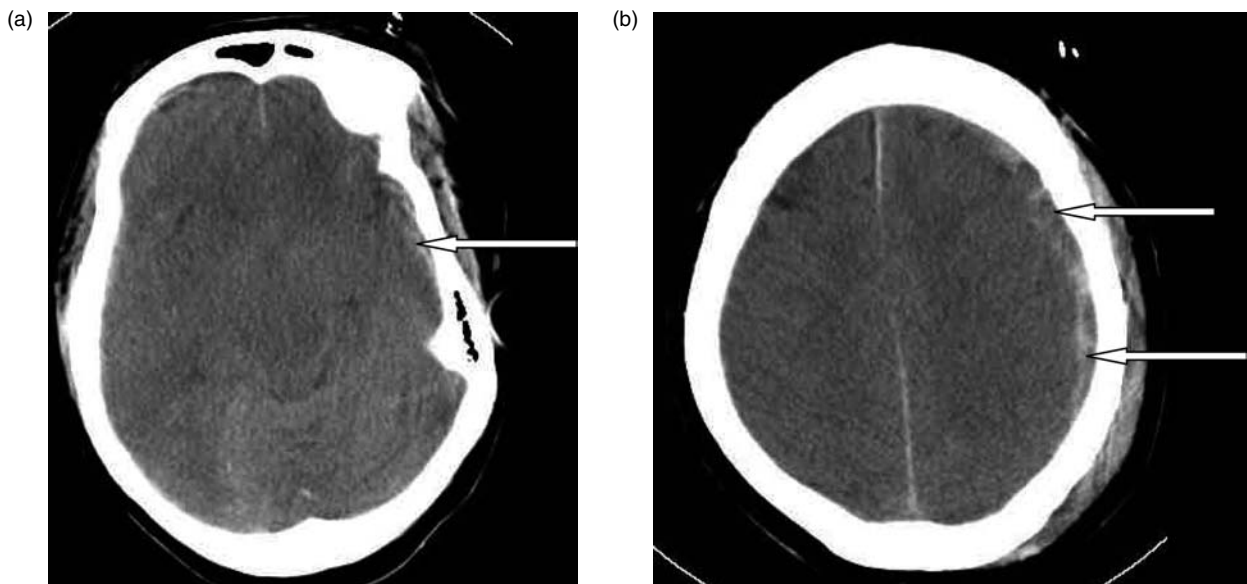
**FIGURE 11-7**

Herniation: Axial noncontrast CT demonstrates a right fronto-temporal subdural hematoma and right frontal hemorrhagic contusion associated with both subfalcine (arrow) and uncal herniation (arrowhead)

sulci, ventricles and cisterns. The normal appearing gray/white matter interface is also lost and the brain appears somewhat featureless throughout (Figure 11-8). As mentioned earlier, severe brain swelling may lead to herniation syndromes in the craniocaudal axis—transtentorial, or inferiorly through the foramen magnum.

The prior confusion of the term “cerebral edema” stems from the fact that there are many different types of edema that have specific pathophysiology. Cytotoxic edema occurs when there is cell injury, ischemia or death. Ion gradients that maintain cell homeostasis are lost, due to inactivation of the sodium/potassium ATP-ase. When ion gradients cannot be maintained, the cells eventually swell with fluid. An increase in water within the cell results in cytotoxic edema. This may be seen on CT as areas of subtle low density or loss of the normal gray/white interface—usually in a focal area or vascular territory. The visual density of gray and white matter on CT is abnormally uniform. Diffusion-weighted MRI (DWI) is very sensitive for areas of cytotoxic edema. Cytotoxic edema manifests as high signal on DWI sequences, or restricted diffusion (31). DWI has gained widespread use in the work-up of acute stroke, among other abnormalities that demonstrate restricted diffusion. An emerging role for DWI in predicting outcome of patients presenting with traumatic brain injury will be discussed later.

Vasogenic edema occurs when there is an increase in extracellular free water. This often occurs around masses, abscesses or hemorrhages. It manifests on CT and routine



**FIGURE 11-8**

Brain Swelling: Axial noncontrast CT [(a) and (b)] demonstrate a left fronto-parietal subdural hematoma (arrow) and diffuse effacement of sulci and decreased gray/white matter differentiation. These findings are consistent with brain swelling

MRI sequences as fingerlike areas of hypodensity extending from the mass/hemorrhage into the adjacent white matter. Because vasogenic edema is free extracellular water, there is no restricted diffusion on diffusion-weighted MRI sequences. The diffusion MRI sequence and apparent diffusion coefficient (ADC) map, a calculated parameter, can distinguish between cytotoxic edema (irreversible) and vasogenic edema (reversible). Cytotoxic edema is high in signal intensity on DWI and low in signal intensity on the ADC map, while free water or vasogenic edema is low in signal intensity on DWI. DWI has properties that reflect relative  $T_2$  weighting. Thus, anything that is bright on  $T_2$  or FLAIR sequences, may be bright on DWI. This is termed  $T_2$  shine-through. The ADC map image is devoid of  $T_2$  weighting, and should always be checked in the setting of bright foci on DWI, to confirm that restricted diffusion of water is actually present.

Interstitial edema is seen in the setting of hydrocephalus and increased intracranial pressure. There is transependymal resorption of CSF from the dilated ventricles into the periventricular regions. There is also an increase in extracellular free water. On imaging, interstitial edema appears as hypodensity in the periventricular locations.

### Extra-axial: Subdural Collections

Our discussion of the pathophysiology and imaging appearances of brain injury will now turn to the extra-axial space. As discussed earlier, the dura is a layer of tissue intimately applied to the inner table of the skull and periosteum. The arachnoid is a network of tissue between the outer dura and inner pia—which lines the cortex of the brain. A fundamental understanding of the dural vascular anatomy, including the middle meningeal artery and dural venous sinuses allows one to predict the etiology of an extra-axial hematoma (32). The subdural space is a potential space that becomes evident radiologically if there is fluid, hemorrhage or purulent material between the dura and arachnoid. Subdural collections are confined to the dural reflections and will not cross midline, although they may cross sutures. These boundaries are helpful if the collection is small and indeterminate. The midline dural reflection is the falx cerebri. Separating the cerebrum and cerebellum is the falx cerebelli. Subdural collections near the midline or cerebellum, may layer on these dural reflections. Sometimes it is difficult to characterize a collection as subdural or epidural in location. Furthermore, it may be difficult to characterize a hematoma as above or below the falx cerebri. In these instances, the indeterminate collections should be referred to as simply extra-axial.

A subdural hematoma is an extra-axial collection of blood that may occur if there is traumatic injury to the

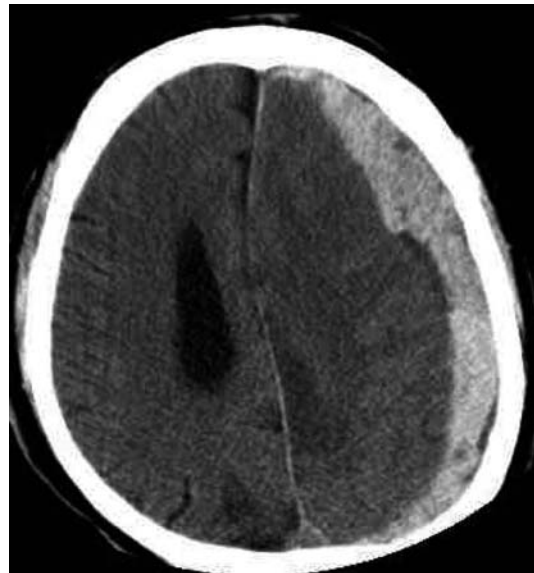


FIGURE 11-9

SDH: Axial noncontrast CT demonstrates an acute left frontoparietal subdural hematoma with mass effect on the underlying cortex

bridging veins beneath the dura (Figure 11-9). These bridging veins travel within the subdural space, toward the main dural sinuses. Acceleration and deceleration forces may lead to tearing of the bridging veins and subsequently, a subdural hematoma. Arterial injury may rarely cause a subdural hematoma. Following vessel injury, blood collects between the dura and arachnoid. An acute subdural hematoma appears hyperdense (bright) on a noncontrast CT of the brain. It is often crescent-shaped and conforms to the inner table of the skull on axial images. Unlike the epidural space that is confined and may exert a tamponade effect to limit the size of the hematoma, subdural hematomas may become large because of the relatively unconfined nature of the subdural space, subarachnoid space and underlying brain. Because subdural hematomas may cross sutures, they are often seen layering along an entire hemisphere. If large enough, these hematomas will exert mass effect on the underlying brain, causing effacement of sulci, ventricles or even midline shift. Severe midline shift may progress to subfalcine herniation as described previously.

The natural evolution of a subdural hematoma may be followed with serial CT scans. The hematoma will become isodense (similar density) when compared to brain, making it difficult to detect between 5–20 days after injury (Figure 11-10). This decrease in density of a subdural hematoma is due to breakdown of hemoglobin and protein products within the collection. These subacute collections are subtle on imaging and secondary signs such as mass effect and sulcal effacement must be searched for in order to diagnose them. Eventually these

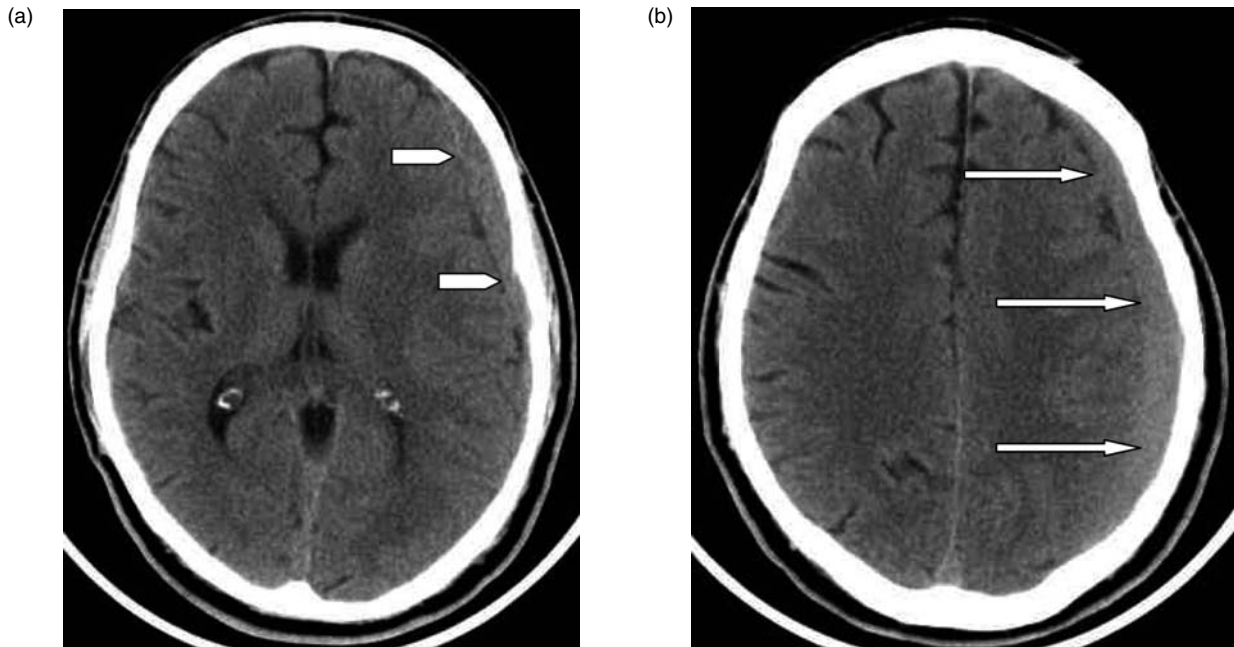


FIGURE 11-10

Subacute SDH: Axial noncontrast CT (10a) demonstrates subtle effacement of sulci on the left convexity (arrowhead). An image more superior (10b) shows the isodense left fronto-parietal SDH (arrows)

collections will become chronic and appear hypodense (dark) compared to underlying brain more than 3 weeks after injury (6, 18). Occasionally, a subacute or chronic subdural hematoma will rebleed, causing a heterogeneous appearance to the collection, with mixed areas of hyper and hypodensity. These collections composed of acute hemorrhage superimposed on chronic blood products appear as a blood-fluid levels in the supine patient. The blood-fluid level is due to differences in density of the blood, or the hematocrit effect. This leads to an appearance of acute, bright blood inferior to the more chronic, serous collection layering dependently.

The mortality rate from traumatic subdural hematomas may be lowered from 90 percent to 30 percent if diagnosis and treatment occur in a timely fashion, usually within the first 4 hr (33). The timing of surgical intervention depends on many factors such as co-existing injuries and the neurological status of the patient. Patients who receive early surgical evacuation of a symptomatic SDH have an improved neurological outcome with relief from increasing intracranial pressure (34).

Subdural hygromas are collections within the subdural space that are hypodense, much like chronic subdural hematomas. They are collections of cerebrospinal fluid (CSF) that result from traumatic leakage from the surface of the brain after injury to the arachnoid membrane (18). It may be difficult to distinguish a chronic subdural hematoma from a subdural hygroma or an expanded extra-axial space. This issue often arises when imaging elderly patients, who have some degree of atrophy and

expansion of the extra-axial spaces. MRI is helpful in these cases, for subdural hygromas and expanded extra-axial spaces will have identical signal characteristics with the CSF in the ventricles and cisterns on all MRI pulse sequences. Subdural hematomas, even if chronic will typically differ from CSF on one or more pulse sequences.

#### Extra-axial: Epidural Collections

The epidural space is another potential space that exists between the inner table of the skull and the closely adherent dura. Collections in the epidural space may dissect between these tissue layers to create an extra-axial epidural collection. Because of the firm attachment of the dura to the inner table of the skull, epidural hematomas tend to be smaller and more confined than the larger, subdural hematomas. Acute epidural hematomas result from injury to the middle meningeal artery or its branches due to fractures of the squamosal portion of the temporal bone (35). Occasionally, acute epidural hematomas contain air within them. These air containing epidural hematomas are associated with fractures that communicate with the sinuses or extra-cranially (36). Ninety-five percent of epidural hematomas are associated with skull fractures and are supratentorial, typically unilateral (1). Injuries of the dural venous sinuses may also lead to epidural hematomas (1). Injuries at the vertex of the skull may lead to disruption of the superior sagittal sinus, creating an epidural hematoma that crosses the midline. The collections typically appear biconvex, much like a lens,

between the brain and skull on axial CT images. Unlike subdural hematomas, epidural hematomas can cross the midline. However, these collections are outside of the dura and cannot cross suture lines, for the dura is firmly attached to the skull at the sutures. If an acute epidural hematoma presents infratentorially, it is usually associated with trauma to the posterior fossa or fracture of the occipital bone (37, 38). An extra-axial hematoma in the posterior fossa is usually epidural in nature and typically unilateral (39). Rarely, acute epidural hematomas may be bilateral in approximately 5 percent of patients (Figure 11-11). When these collections are bilateral, they are often bifrontal in location (40).

Approximately one-third of patients with epidural hematomas are lucid clinically prior to neurological deterioration (35). Like all other forms of acute hemorrhage on CT, acute epidural hematomas are hyperdense (bright) compared to brain. These hematomas evolve to become isodense, then hypodense (dark) compared to brain over several days to weeks. Like any extra-axial collection, epidural hematomas will exert mass effect on the underlying brain and result in effacement of sulci and ventricles. When severe, these collections present with midline shift and herniation. In contrast to a peripherally located hemorrhagic contusion, epidural hematomas will typically form obtuse angles with the underlying brain, revealing their extra-axial location.

The mortality rate is lower for epidural hematomas (10 percent) when compared to subdural hematomas. The reported mortality rate is variable and ranges from

20 to 90 percent (1, 35, 41). Because of firm dural attachments, there is usually a tamponade effect for epidural hematomas, while subdural hematomas are less confined and may be larger or appear in a delayed fashion as discussed above. Most epidural hematomas are acute and are detected during the initial imaging work-up. Occasionally a patient may present subacutely with a delayed epidural hematoma. About 6–13 percent of epidural hematomas are delayed in presentation while some authors have reported this as high as 30 percent (42).

### Extra-axial: Subarachnoid Hemorrhage

The subarachnoid space is the CSF containing space between the arachnoid membrane and the pia that covers the brain. CSF originates in the choroids plexus and flows from the ventricular system to the basilar cisterns, then finally to the surface of the brain. CSF is then absorbed by the small arachnoid granulations within the dural venous sinuses. CSF bathes the brain surface and extends into the sulci.

Subarachnoid hemorrhage (SAH) most commonly (90 percent) occurs secondary to a ruptured aneurysm involving the Circle of Willis. Usually subarachnoid hemorrhage secondary to a ruptured aneurysm is larger than bleeding caused by trauma. The locations are different as well. A ruptured aneurysm typically has most of the blood near the site of rupture. For example, if the aneurysm is located in the Circle of Willis, the basal cisterns usually fill with blood. Traumatic subarachnoid hemorrhage is

(a)



(b)



FIGURE 11-11

Acute EDH: Axial noncontrast CT (11a) demonstrates bilateral, biconvex epidural hematomas (arrows). An image more superior (11b) shows a large right-sided EDH with mixed, swirling density suggesting active bleeding

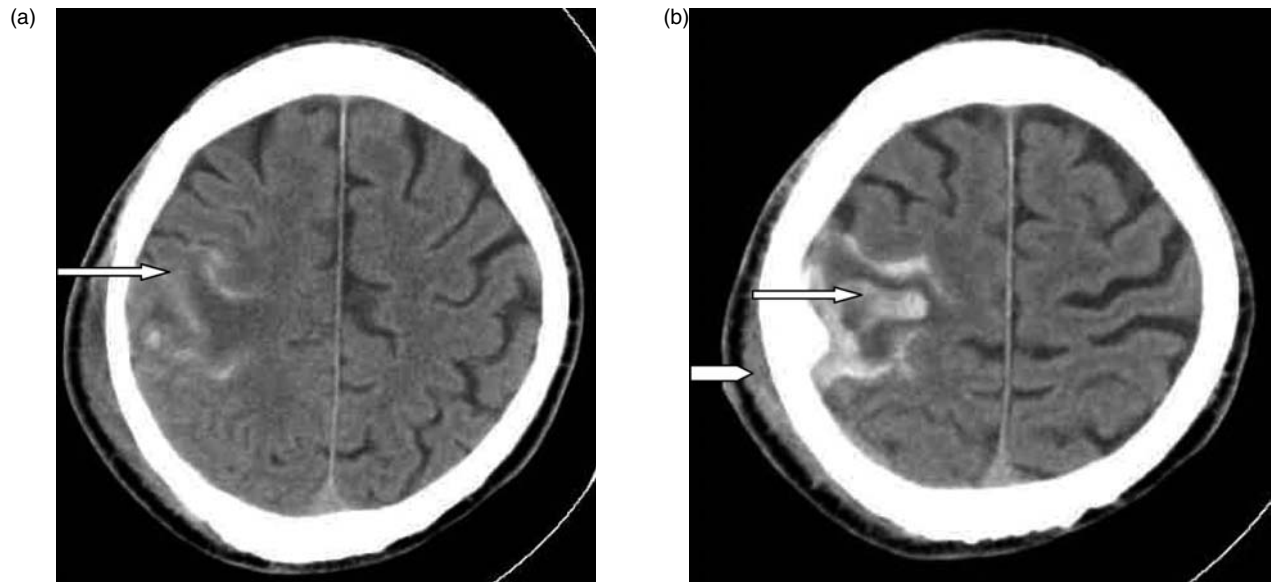


FIGURE 11-12

SAH: Axial noncontrast CT images [(a) & (b)] demonstrate traumatic subarachnoid hemorrhage filling right-sided sulci (arrows). Also note the right scalp soft tissue swelling (arrowhead)

much more variable in location. SAH presents on CT as hyperdense blood within the sulci (Figure 11-12) or basal cisterns. CT is very sensitive for the detection of acute SAH (18). MRI is less sensitive for the detection of acute SAH, however is very good for imaging chronic blood products or hemosiderin.

Besides a ruptured aneurysm or trauma, other causes of subarachnoid hemorrhage include arteriovenous malformations and coagulopathies (23). There are also many complications that may occur with SAH and follow-up imaging is recommended. These include vasospasm, stroke, communicating hydrocephalus, and arachnoiditis. MRI imaging in patients with SAH may show blood products in varying stages within the sulci or cisterns. Fluid attenuated inversion recovery (FLAIR) sequences employ a longer T1 and a 180-degree inversion pulse to reduce the signal level of CSF and detect abnormalities in the sulci such as SAH with a greater degree of certainty (5). As described earlier, chronic SAH may present on gradient echo or magnetic susceptibility sequences as leptomeningeal hemosiderosis—hypointense (dark) meninges on  $T_2$ -weighting (23).

#### Extra-axial: Intraventricular Hemorrhage

The intraventricular space is a CSF-containing space within the paired lateral, third and fourth ventricles. Intraventricular hemorrhage (IVH) may occur within any ventricle; however, often occurs in the lateral ventricles after trauma. It may be a primary event or secondary event such as extension from a parenchymal contusion or

existing SAH. Primary IVH in the trauma patient is due to injury of the subependymal veins surrounding the ventricles. As described for mixed subdural hematomas with blood–blood levels, the acute intraventricular hematoma will layer in the dependent portions of the ventricle in a supine patient. If the hemorrhage is within the lateral ventricle, the blood is often seen in the occipital horns posteriorly. It has been reported to occur in 35 percent of patients with moderate to severe brain injury (1, 35). IVH may lead to a non-communicating hydrocephalus (described below) due to obstruction of CSF flow at the level of the foramina of Monro or the cerebral aqueduct (Figure 11-13).

#### Extra-axial: Hydrocephalus

Hydrocephalus is dilatation of the ventricles that contain cerebrospinal fluid (CSF). It involves an increase in the volume of CSF within the subarachnoid space, ventricles and cisterns (14). Ventriculomegaly is a generic radiological term meaning enlargement of the ventricles, while hydrocephalus implies a pathologic state that may lead to elevated intracranial pressure. Cerebral atrophy or old age may cause ventriculomegaly secondarily. The CSF-spaces dilate to compensate for the loss in brain parenchyma over time. Patients over the age of 65 usually have some degree of brain volume loss, or atrophy. The enlargement of the ventricles in this case is termed hydrocephalus ex vacuo. The ventricles, sulci and cisterns appear larger radiologically because of underlying brain parenchymal loss. Hydrocephalus ex vacuo occurs





**FIGURE 11-13**

IVH: Axial noncontrast CT demonstrates intraventricular hemorrhage filling the third and lateral ventricles (arrows). There is also hydrocephalus present

physiologically and does not result in elevated intracranial pressure.

There are two types of pathological hydrocephalus: communicating hydrocephalus and noncommunicating hydrocephalus. In these conditions, there is an increase in CSF volume without brain atrophy. Communicating hydrocephalus is a global dilatation of all of the ventricles, while the connections between the ventricles remain patent. Typically, there is disruption of CSF reabsorption at the level of the arachnoid granulations of the dural venous sinuses. Conditions that cause communicating hydrocephalus include subarachnoid hemorrhage, meningitis and meningeal carcinomatosis (23). Communicating hydrocephalus can be differentiated from hydrocephalus ex vacuo by signs of elevated intracranial pressure and radiologically by dilated ventricles in the setting of cisternal and sulcal effacement.

Increased production of CSF may also cause communicating hydrocephalus, as in normal pressure hydrocephalus (NPH) and tumors of the choroid plexus. Prior to sampling CSF, clinicians often obtain an imaging study, usually a noncontrast CT of the brain to evaluate for hydrocephalus or mass effect. If too much CSF is removed in the acute setting, intracranial hypotension or herniation syndromes may develop (43–45).

Noncommunicating hydrocephalus is a condition in which there is obstruction of the ventricular system

somewhere between the lateral ventricles and the fourth ventricle. Congenital causes such as cerebral aqueductal stenosis may result in dilated lateral and third ventricles. Intraventricular hemorrhage, meningitis and infection may also result in obstruction of the ventricles. Obstruction may also occur at the level of the foramina of Monro leading from the paired lateral ventricles to the midline third ventricle. Thus, non-communicating hydrocephalus would be expected to cause asymmetric dilatation of the ventricles, while communicating hydrocephalus causes diffuse dilatation of the ventricular system on MRI and CT.

### IMAGING: PREDICTING OUTCOME

As mentioned at the beginning of this chapter, it is important to understand the pathological conditions that occur within the skull and brain and the appearances of these injuries on CT and MRI. As the technology improves, the lexicon used for discussing imaging findings may change, however the pathology will not change. It is important to realize the limitations of CT and MRI and many injuries are currently beyond the resolution of any imaging modality. To review, CT is the initial imaging modality of choice in traumatic brain injury. The routine emergency non-contrast CT of the brain allows clinicians to rapidly decide if an injury requires emergent surgery, delayed surgery or only medical therapy.

CT also provides indirect signs of increased intracranial pressure through compression of brain stem cisterns, compression of the ventricles, midline shifts, and loss of gray-white matter differentiation (46). Because CT can be performed so quickly, there is less opportunity for motion artifacts that can ruin a study. In addition, there are essentially no contraindications other than an unstable patient, and CT can also be performed in patients with extensive life-support hardware.

After the initial work-up and management of neurologically traumatized patients occurs in the emergency room or intensive care unit settings, decisions must be made that concern the post-acute management of these patients. extra-axial collections, large contusions, midline shift and herniation syndromes are readily diagnosed with routine CT, and will allow the emergency room physician to appropriately triage these patients to surgery. As described previously, diffuse axonal injury (DAI) is often a neurologically devastating injury that may be missed in CT imaging. A normal CT scan in a patient that is comatose after sustaining traumatic brain injury is a classic finding. This is one of the reasons why clinical presentation and imaging are complementary and must be correlated with each another.

In a series of 448 patients with a GCS below 8, 70 patients had a normal CT scan on the day of admission and 47 of these remained normal with serial scanning.

This number represented 25 percent of those with DAI. Although 76 percent of those with normal scans made a good recovery, 19 percent had coma persisting longer than 2 weeks with subsequent severe disability. Brain atrophy at 6 months was a common result, despite the initial normal CT scan, implying diffuse injury. Delayed lesions (usually contusions) occurred in 24 patients, of which 9 had no clinical deterioration. Therefore, although a normal CT scan may be obtained initially in a patient with severe traumatic brain injury, abnormalities on serial imaging may evolve even in the absence of clinical deterioration. Likewise, abnormalities on CT imaging may appear in patients with very mild head injuries with few if any clinical findings (46).

To date, there is no agreed upon classification system for patients with head injury, the severity of clinical presentation, and the findings on imaging. Several different schemes, however, have been evaluated. One such classification is the National Traumatic Coma Data Bank (TCDB). This classification scheme is based on a multicenter study of patients with severe, blunt, traumatic head injuries. Clinically, all of these patients had a Glasgow Coma Scale of less than 8. The TCDB in these patients focused on the imaging findings of basal cistern effacement and midline shift, with the operative findings to predict mortality (47). Caroli et al identified several clinical and radiologic predictors of prognosis in patients with multiple post-traumatic intracranial lesions. The type of lesion—such as subdural hematoma or intracerebral hematoma, the Glasgow Coma Scale (GCS), the presence of prolonged increased intracranial pressure, and the absence of pupillary reflexes were found to all be statistically significant predictors of a poor outcome. Poor outcome in these patients was defined as death or a persistent vegetative state. The authors concluded that multiple lesions have the same prognosis as the corresponding single lesions and that management should be guided by the predominant pathology (48).

Toutant et al. noted that assessment of the basal cisterns can be used as an early noninvasive method to assist in determining prognosis. Compression of the basal cisterns in patients with traumatic brain injury was associated with a high mortality rate in both surgical and nonsurgical patients. One-hundred percent of the deceased patients had cistern compression. The mortality rates were 77 percent, 39 percent, and 22 percent among patients with absent, compressed, and normal basal cisterns, respectively (49). Lannoo et al. studied patients with severe brain injury and the resulting mortality and morbidity in relation to age, and early (< 24 hr) clinical data and the imaging findings after CT. Patients with traumatic injuries to parts of the body other than the brain were used as controls. Of the group with traumatic brain injury, the mortality rate was 51 percent. Analyses combined 13 predictors into a model with an accuracy

of 93 percent, a sensitivity of 90 percent, and a specificity of 95 percent. These 13 predictors included the following: 1, age; 2, GCS score; 3, pupillary reactivity; 4, blood pressure; 5, ICP; 6, blood glucose; 7, platelet count; 8, body temperature; 9, cerebral lactate; and 10, subdural; 11, intracranial; 12, subarachnoid; and 13, ventricular hemorrhage. Further analysis resulted in the GCS score being the best predictor of neuropsychological functioning, and pupillary reactivity being the most predictive for self-reported quality of life. Those factors important for predicting mortality such as elevated intracranial pressure and the CT observations failed to show any significant relationship with morbidity (50).

The anatomical location and mechanism of injury to the brain are crucial factors in determining future neurological functioning of patients. CT is the imaging study of choice in patients presenting acutely with penetrating injuries to the brain. Gonul et al. studied 35 patients presenting with penetrating orbitocranial gunshot injuries. This group found that anatomical location of injury, extent of injury and GCS score at presentation were the most important predictors of neurologic recovery following penetrating orbitocranial injuries (51). The anatomical location of an injury as determined by imaging also has implications on patient outcome. Blackman et al. evaluated the anatomical location of injuries involving 92 patients presenting with acute traumatic brain injury. They defined several levels of injury progressing from the cortex of the brain to the brainstem, a depth of injury level. Images were classified according to five depth of lesion levels (cortical to brainstem). Functional outcomes in mobility, self-care, and cognition were evaluated in conjunction with the depth of lesion encountered on imaging. Patients with deeper (brainstem) lesions tended to have longer lengths of stay in rehabilitation, however were able to eventually become equal with patients who had more superficial lesions. The authors suggested that one may not be able to predict outcome in the early acute phase in the intensive care unit on the basis of standard brain imaging alone. Patients with deeper lesions tended to enter rehabilitation at a more impaired level, although may eventually reach a level of functioning equal to peers with more superficial brain injuries. They also suggest that it may take a longer period of time to reach this level of functioning than for less severely injured individuals (52).

While many studies have evaluated the Glasgow Coma Scale or compared a different scale to the GCS, some authors have suggested that the 15-point GCS may not add any additional prognostic value over more simplified triage scales. Gill et al. evaluated the performance of GCS scores in a level 1 trauma center from 1990 to 2002, relative to four clinically relevant traumatic brain injury outcomes (emergency intubation, neurosurgical intervention, brain injury, and mortality). They evaluated

a simplified 3-point scoring system (simplified verbal score: oriented = 2, confused conversation = 1, inappropriate words or less = 0; simplified motor score: obeys commands = 2, localizes pain = 1, withdrawal to pain or less = 0) with the total GCS and found that the simplified scoring system correlated well with the GCS for predicting outcome. This study suggests that the 15-point GCS may be needlessly complex for predicting neurological outcome (53).

While CT is most important in the acute triage of patients with traumatic brain injury, MRI is more helpful in evaluating the long-term sequelae of these patients. The value of MRI in predicting outcome of rehabilitation in patients with head injury appears promising in view of the relationship between MRI abnormalities and neuropsychological deficits (54). Post-traumatic seizures (PTS) and post-traumatic epilepsy (PTE) are well-documented sequelae of traumatic brain injury. Patients who have depressed skull fractures, acute intracranial hematomas, or seizures during the first week post-injury have an increased risk of developing PTE. Factors found to influence the likelihood of seizures include severe head injury (GCS 3 to 8), diffuse cerebral edema, acute SDH and depressed skull fractures (55). Information obtained through static neuroimaging techniques, and particularly MRI may help identify patients at increased risk for PTS or PTE (56, 57).

Mazzini et al. detected the risk factors for PTE in rehabilitation patients and found that the occurrence of PTE was significantly correlated with hypoperfusion in the temporal lobes, the degree of hydrocephalus, the evidence of intracerebral hematoma, and operative brain injury. Hypoperfusion in the temporal lobes was determined with single photon emission computed Tomography (SPECT), while hydrocephalus was diagnosed with MRI. This study sought to define the influence of PTE on late clinical and functional outcome. Findings revealed that the psychometric tests intended to explore memory, language, intelligence, attention, and spatial cognition did not show any significant difference between patients with and without epilepsy. PTE also was significantly correlated with a worse functional outcome 1 year after the trauma (58).

Pohlmann et al. identified clinical and neuroradiological variables in severe brain injury with predictive value for PTE and evaluated the influence of each risk factor for epilepsy. The authors found that of all patients with PTE in the study, 68.5 percent had their first seizure within two years after the trauma. Significant risk factors for PTE were focal signs in the first examination, missile injuries, frontal lesions, intracerebral hemorrhage, diffuse contusion, prolonged posttraumatic amnesia, depression fracture and cortical-subcortical lesions. The combination of the last three variables conferred a particularly high risk for PTE.

The authors concluded that the risk for PTE is clearly determined by variables that correlate with the severity, the extent of tissue loss and the penetrating nature of the brain injury. Combined seizure pattern, high seizure frequency, anti-epileptic drug noncompliance and alcohol abuse predicted poor seizure control (59).

While the use of MRI is well established in evaluating patients that present with PTE, some researchers have also studied the role of diffusion weighted MRI (DWI) in traumatic brain injury. As discussed earlier with cerebral edema, diffusion-weighted MRI (DWI) is very sensitive for areas of cytotoxic edema. Diffusion MRI is a sequence that has become very important in the imaging of acute and subacute stroke. It allows one to distinguish between cytotoxic edema that is present in cerebral infarction from vasogenic edema. In addition, the diffusion MRI helps to define at risk tissue and often is positive before the patient has CT findings to indicate a stroke. Schaefer et al. evaluated 26 patients presenting with diffuse axonal injury using diffusion weighted MRI. They found that the volume of lesions on diffusion-weighted MRI provides the strongest correlation with a score of subacute on modified Rankin scale at discharge (60). Goetz et al. evaluated 23 patients with traumatic brain injury using diffusion weighted MRI and specifically studied the role of the apparent diffusion coefficient (ADC). The ADC is a parameter used in diffusion MRI to distinguish between true diffusion restriction suggesting cytotoxic edema vs. "T2 shine-through," or anything that may have increased signal on T2 weighted sequences. These researchers found reported a correlation between injury severity and increasing ADC ( $p = 0.03$ ) but no correlation with either T1 or T2 weighted MRI, suggesting that the ADC used in diffusion MRI is a sensitive and independent marker of diffuse white matter tissue damage following traumatic insult (61).

Many of the studies discussing the use of MRI, and particularly diffusion MRI (DWI) have focused on subacute or chronic traumatic brain injuries. Some authors have also explored the use of MRI in the acute setting. Maeda et al. evaluated 10 patients with diffusion-weighted MRI, presenting in the acute setting with traumatic brain injury. Their study attempted to define the time frame for development of cerebral edema following acute brain injury. Within 3 hr post-trauma, diffusion MRI showed no remarkable pathology. Furthermore, the ADC values at 3 hr post injury were within the normal range (contused/normal brain =  $1.00 \pm 0.21$ ). At 6 hr post-injury, diffusion-weighted MRI demonstrated a low signal intensity core in the contusion and a high signal intensity rim in the peripheral area of contusion. The ADC value at 6 hr increased in the contusion proper (contused/normal brain =  $1.26 \pm 0.13$ ) and decreased in the peripheral area (contused/normal brain =  $0.58 \pm 0.19$ ). These findings indicated that early cellular swelling in the

peripheral area of contusion begins within 6 hr following injury. The authors also propose that the delayed occurrence of contusion-induced cellular swelling suggests that the cerebral blood flow does not decrease to ischemic levels immediately following injury (62).

Static imaging techniques may also be used to follow patients with brain injury for potential delayed complications. As discussed earlier, hemorrhagic or non-hemorrhagic contusions may occur in the brain due to blunt forces. The frontal and temporal lobes are particularly vulnerable to contusions secondary to the underlying bony ridges. Delayed bleeding may occur into these regions of perfused yet injured brain. These delayed complications may lead to neurological deterioration from edema, increasing mass effect, and herniation. Delayed hemorrhages into the orbital-frontal regions may also lead to neurological deterioration due to elevated intracranial pressure. Early diagnosis and aggressive therapy in these patients could potentially improve outcome (63). Several authors have examined the sequelae of delayed intra-cerebral hemorrhage and the role that static imaging plays (64, 65). Delayed intra-cerebral hemorrhage often occurs between 3 hr and 10 days after the inciting traumatic insult, particularly within the first 3 days. Thus, if these potential lesions are deemed clinically significant, static imaging performed within this time interval is likely to detect these delayed complications. There have been case reports of patients presenting with delayed hemorrhages as long as 168 days post-trauma (66). These occurrences are the exceptions rather than the rule. These delayed lesions may present with non-focal symptoms such as headache or vomiting. Thus, delayed intracerebral hemorrhage may be considered in the differential diagnosis in these patients if there has been a recent history of trauma.

## CONCLUSION

This chapter has focused on the predominant static imaging modalities used in the evaluation of traumatic injury of the brain. In addition, the dominant injuries seen in clinical practice have been described, and their appearances on imaging have been reviewed. These injuries and their sequelae have been discussed in terms of clinical outcome.

In summary, imaging technology is rapidly progressing. There are advances being made daily in the fields of imaging physics, computers, computed tomography, and magnetic resonance imaging. These modalities become the tools that may be used by imagers and clinicians to evaluate, diagnose and treat traumatic injuries of the brain. What does not change, however, is the pathophysiology of brain injury. Thus, it is of paramount importance to learn the mechanisms, anatomy, physiology, and evolution of the different manifestations of traumatic brain injury.

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# 12

## Functional Neuroimaging of TBI

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### INTRODUCTION

New technologies, as well as advances in existing technologies, have changed how both healthy and injured brains are evaluated in research and clinical settings. In combination with traditional neuromedical examination and psychometric testing, functional neuroimaging is providing a means through which additional information about brain structure, function, and recovery may be obtained. Enthusiasm for functional neuroimaging can be readily appreciated, yet it must be balanced by the need for empirical evidence and a healthy level of caution.

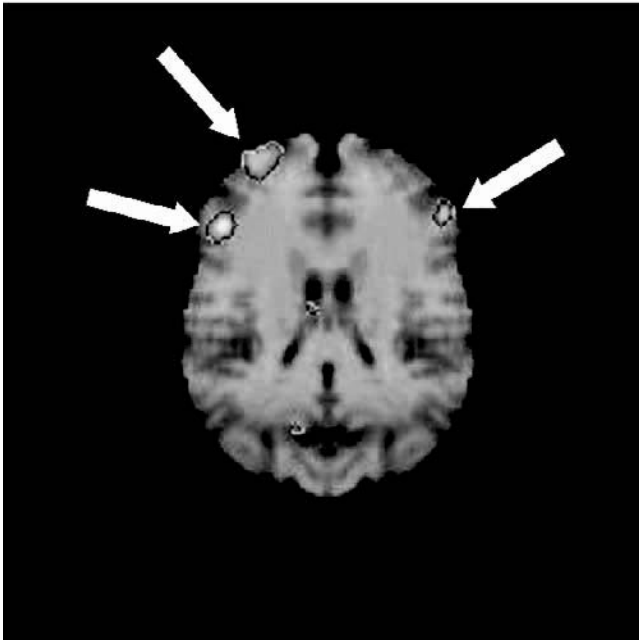
Increasingly, clinicians are using advanced imaging techniques (e.g., SPECT, PET, fMRI) with persons having traumatic brain injury (TBI), however, clinical application of most of these techniques still remains investigational, within the context of this population (1). The present chapter provides an overview of several functional neuroimaging procedures and their applications in the context of TBI. This chapter will also address many limitations of these procedures, with implications for exercising caution if they are utilized in clinical evaluation.

### RESTING AND ACTIVATED FUNCTIONAL NEUROIMAGING

In functional neuroimaging, one can dichotomize the available techniques into two broad categories: “resting”

or “activated” (2). Resting paradigms are those that acquire functional images during nonactivated (i.e., “static” or baseline) conditions. Resting studies, by design, have no explicit or systematic requirements of the participant other than those required to successfully acquire a technically valid image, such as having the participant lie still, minimizing head movement, and eliminating extraneous stimuli (3). Although participants do not overtly engage in any specific task, there is no systematic way to “control” random or volitional covert mental activity during the image acquisition. There have been several studies that have applied resting functional neuroimaging across multiple populations, most of which have examined chronic glucose uptake (with positron emission tomography, PET), and resting cerebral blood flow (using PET or single photon emission computed tomography, SPECT). These studies will be discussed later in context.

In contrast to resting paradigms, activation studies require participants to systematically receive sensory input (e.g., a visual array) or engage in an activity (e.g., motor or cognitive) in order to elicit changes in brain physiology that are correlated with a specific stimulus or event in time (4). These tasks are usually administered in adherence to a strict protocol, typically with some form of overt response required in order to provide an objective correlate of the participant’s active engagement in the task. Because of the physical properties of the dependent



**FIGURE 12-1**

An Example of O-15 PET Combined with an Activation Paradigm. The participant is being asked to recall a previously learned list of words while being scanned. Regions of increased blood flow (indicated by the arrows) within the frontal lobes are associated with increased cerebral activity known to mediate retrieval of newly learned information

variables examined (e.g., briefer half-lives of radioisotopes, or transient changes in hemodynamic response), activation studies have much briefer time sampling windows than resting studies. Some technologies are even able to image changes across time in a relatively continuous manner (e.g., magnetoencephalography and event-related functional MRI). Given this improved level of control, activation studies permit examiners to make more accurate inferences about the cerebral activity correlated with the motor or cognitive process in question. Figure 12-1 presents an example.

### **SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT)**

SPECT is an approach to functional imaging that is based on the concept that regional changes in brain activity or chemistry can be measured indirectly via externally placed gamma radiation detectors (referred to as “cameras”), which detect the regional accumulations of tracer flow or receptor-binding isotopes. There is an emphasis on imaging changes in regional cerebral blood flow (rCBF), but relatively specific neuroreceptor imaging studies are also possible using SPECT (5).

The dependent variable in SPECT derives from the well-established principle of increased cerebral activity

correlating with increased blood flow. That is, when neural activity in a region of the brain increases, related energy requirements also increase. Because the blood supply carries glucose and oxygen to the brain, the flow of blood to the active area increases (6). The radioisotopes themselves are absorbed into glial cells that are proximal to the active neurons, but these isotopes are not immediately excreted. Thus, the absorbed radioisotopes remain in greater concentration in the more active areas. Through normal radioactive decay, the isotope emits annihilated radioactive particles (i.e., photons), which are then detected by the external cameras. Computer-based reconstruction permits external representations to be derived that correlate with differences in blood flow.

SPECT is more widely available than PET or FMRI. In addition, many of the radioisotopes that are typically used with SPECT can be ordered and delivered in advance, thus precluding the necessity of an on-site cyclotron and chemist, as required for PET. SPECT has application in examining resting blood flow, but has more limited utility in imaging a change in blood flow from one point in time to another. SPECT can be used to image change in resting blood flow from one well-defined event to another (e.g., from pre-ictal to ictal state), but it is not appropriate for use in mapping blood flow changes that change rapidly over time (such as those encountered in most states of cognitive activity), or for making direct inferences about brain metabolism (4) due to the time require for radioactive decay of the isotopes: The most commonly used radioactive isotopes for SPECT are absorbed by the brain within 2 min, but may have half-lives of several hours. The effect of this is that after the tracer has been administered, the resulting images that may be acquired can remain the same for the next several hours.

SPECT is not as diverse as other imaging techniques, such as PET, but novel ligands are under continuous development. The compound 123-I-para iodoamphetamine (IAMP) provides a unique look at immediate and delayed perfusion. Other compounds such as 99m-Technetium-HMPAO are also being used for the same purpose. Recent technologic advances have provided for multiple-headed scanners, which offers improved spatial resolution.

As with all assessment tools SPECT has several sources of potential measurement error. Unlike PET, SPECT imaging requires that regional counts be normalized to an area that is ostensibly free from injury. Thus, *relative* flow values in SPECT are often based upon a region such as the thalamus or cerebellum. While such assumptions might be valid for some populations with focal lesions (e.g., stroke), they might not be valid for populations whose neuropathology is more diffuse, such as occurs in TBI. In addition, SPECT resolution currently does not yet approach that of PET imaging. Color SPECT

imaging software can produce visually striking – but potentially misleading images, thus reliable and valid interpretation is best accomplished through quantitative pixel counts (7). It must also be noted that although SPECT *can* be used quantitatively, this is not the case in most clinical settings. Visual inspection of SPECT maps is a subjective, qualitative process, and interpretation may vary from clinician to clinician (8).

### SPECT STUDIES OF BRAIN INJURY

Resting brain SPECT studies of individuals acquired months (or sometimes years) after moderate and severe brain trauma have demonstrated decreased cerebral blood flow, primarily within prefrontal cortex (9–10). In most of these studies, decreased blood flow and metabolism were generally beyond what might be expected based solely on findings from structural scans (i.e., CT and MRI). The presence of decreased resting blood flow or metabolism is not, however, in and of itself evidence of compromised or nonfunctional brain tissue (11).

Numerous investigations have demonstrated that SPECT is superior to CT and structural MRI in the detection of the presence and extent of trauma-related lesions. SPECT has been applied to mild brain injury and has demonstrated regionally decreased blood flow in the presence of normal acute CT scans, but there is much variability across individuals (i.e., no pathognomonic profile emerges). Positive SPECT findings have also sometimes been demonstrated in cases of below average neuropsychological test scores in cases of mild brain trauma, but it should be noted that SPECT findings are usually not very predictive of neuropsychological test performance (12–13).

In spite of advances in technology and data analysis, the utility of SPECT in characterizing specific injury states or predicting outcome remains controversial. SPECT has been shown particular utility when correlating neuropsychological parameters with the effects of brain injury (14–15), but caution must be exercised given that SPECT findings are routinely positive in a variety of medical and neurological disorders (16–19), learning disabilities (20), as well as in substance use and emotional disorders (e.g., 21–30). Some investigators have noted that when used in a *prospective* design, a negative SPECT scan is a good predictor of a favorable outcome after brain injury, and that SPECT overall correlates well with the severity of the initial trauma (31). Still, there are relatively few well-controlled prospective studies of SPECT (and for that matter, PET and fMRI) being used in differential diagnosis, prognosis, and intervention (2, 32). The use of normative data (8), rather than subjective impressions of SPECT images, will greatly facilitate such developments.

SPECT has been shown to be of use in research studies following brain injury, but there is no particular SPECT profile that is solely pathognomonic for any level of traumatic brain injury (2, 33). The Therapeutics and Technology Subcommittee of the American Academy of Neurology (34) rated SPECT as an *investigational* procedure for the study of brain trauma. More recently, the American College of Radiology (ACR) (1) has rated SPECT as inappropriate (a rating of 2 on a scale of 1 to 9, with 1 indicating “least appropriate”) in clinically evaluating postconcussion symptoms. In spite of the absence of evidence supporting routine use of SPECT in brain injury, SPECT appears to be used frequently in clinical and forensic contexts as a means of supporting a diagnosis of brain injury. With increasing evidence and appropriately designed studies, however, and greater specificity of diagnostic criteria (particularly with mild head injury), SPECT is likely to be of improved clinical utility in the future (32, 35–36). For example,  $^{99m}\text{Tc}$  SPECT has been used recently to examine the therapeutic effects of hyperbaric oxygen on recovery after TBI (37). SPECT has also recently been found to be predictive of post-traumatic amnesia acutely after TBI (38) and useful in assessing the efficacy of intraventricular shunt placement after TBI (39).

### POSITRON EMISSION TOMOGRAPHY (PET)

Like SPECT, positron emission tomography (PET) is a radioisotope-based imaging technology. PET studies typically utilize intravenous tracers such as  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) for the quantification of “resting” (i.e., nonactivated) regional brain metabolism (40). An exception is Xenon, which is an inhaled isotope. As they are catabolized, annihilation particles are emitted and are detected by an external scanner.

Resting blood flow changes (41) and dynamic changes associated with motor or cognitive activity (11) can be accomplished through the use of tracers such as oxygen-15 ( $\text{O-15}$ ) labeled water. Radiolabeled ligands that bind selectively within dopaminergic, serotonergic, and other endogenous neurochemical systems have been developed and are seen as having great potential for future research (36). Genetically mediated transporter markers (e.g., for dopamine transport) are also available (42).

PET has been widely used as a research tool since the 1970s, but requires a cyclotron to be present on site for most radioisotopes and remains a very expensive procedure. Thus, its application to persons with traumatic brain injury has been minimally investigated. PET has the capability of demonstrating specific biochemical or physiologic processes associated with cerebral blood flow and metabolism. As with SPECT, clinical data from PET



imaging are typically portrayed visually in the form of the spatial distribution of radioisotopes projected on to actual or standardized anatomic MRI templates.

### PET STUDIES OF BRAIN INJURY

Acute O-15 PET studies of human brain trauma have shown that significant changes in regional (but not necessarily global) hemodynamics occur, such as lower contusional and pericontusional blood flow and flow-to-volume ratios (43). There is also heterogeneity in regional glucose metabolism (44). In addition, cerebral hyperglycolysis is a pathophysiological response that occurs in response to injury-induced neurochemical cascades and can be demonstrated via FDG-PET (45–46).

Several studies have demonstrated PET's ability to detect brain abnormalities that are not visualized on CT or standard MRI sequences in cases of moderate and severe brain injury (2). In addition, functional imaging data exist to suggest that there can be regions of physiological dysfunction beyond the boundaries of static lesions (e.g., contusions) seen with structural imaging. This has been demonstrated for many years using both FDG-PET (47) and Cobalt-55 PET (48). Such changes are seen acutely and occur more in grey matter relative to white matter (49). Acute metabolic changes often begin to resolve within the first month following injury, regardless of injury severity, but the correlation between the extent of change in disability and the changes in brain metabolism are minimal (46).

Although PET would appear intuitively to lend itself well to the many clinical issues that emerge after brain trauma, there are surprisingly few studies that have actually attempted to directly relate functional imaging findings with cognition after TBI. In most of these studies, the findings from neuropsychological and other assessments have been obtained at points in time that were quite disparate from the time at which imaging occurred. For example, one frequently cited paper (50) described FDG-PET and neuropsychological test scores among a selected group of 9 individuals that had experienced mild head trauma. Their CT and MRI findings were negative, but PET imaging demonstrated a variety of regions of decreased FDG uptake, some (but not all) of which corresponded to decreased cognitive testing scores. Such findings have little generalizability, however, given that subjects were specifically selected for inclusion based upon their outcome criteria rather than criteria selected a priori. In addition, scanning and the neuropsychological evaluation were separated in time by an average of 11 months, thus essentially negating the reliability of any correlation between PET and cognitive findings.

In more carefully designed studies, it has been noted that localized abnormal cerebral metabolic rates in

frontal and temporal regions correlate with both subjective complaints and neuropsychological test results obtained during the chronic phase of recovery (51). In moderate and severe TBI, resting PET studies have demonstrated frontal hypometabolism, with related decreased performance on neuropsychological tests that are mediated by frontal lobe functioning (52). Recently, through the use of PET, an association between post-TBI anosmia and orbitofrontal hypometabolism has been demonstrated (53).

As described earlier in this chapter, activation studies are likely to be far more sensitive to the functional effects of brain injury or disease, as such paradigms introduce *in vivo* cognitive challenges (54). The first published PET study (55) to apply a cognitive activation paradigm with individuals that sustained brain injury demonstrated cerebral blood flow changes in the left prefrontal cortex among individuals with TBI during a free recall task when compared to controls, but blood flow increases were noted in more posterior brain regions in TBI subjects during both free and cued recall. The change in allocation of neural resources during tasks with greater cognitive load may suggest increased cognitive effort among individuals with TBI (and thus greater blood flow within prefrontal cortex during task performance). In addition, it was demonstrated that during recognition tasks, both the controls and the individuals with TBI performed at comparable behavioral levels (and within normal limits), yet the individuals with TBI still demonstrated increased change in regional cerebral blood flow relative to the controls. This suggests that after brain injury, individuals must exert more cognitive effort than controls to attain the same level of overt behavior. Subsequently, a different group of investigators also demonstrated comparable findings in a larger sample of individuals with TBI, again using O-15 PET and a verbal memory task (56).

### FUNCTIONAL MAGNETIC RESONANCE-BASED IMAGING (FMRI)

Techniques based on magnetic resonance imaging (MRI) capitalize on the presence of hydrogen in all of the body's tissues. When the nuclei of hydrogen atoms encounter a strong magnetic field, they align in parallel to that field's direction. In MRI, radiofrequency (RF) pulses are presented at an angle that is at 90° relative to the magnetic field. This causes roughly 1 percent of the hydrogen nuclei to realign and begin spinning in a different direction (a condition called "excitation"). When the RF pulse is then stopped, the nuclei return to their original alignment and spin (57). During the process of returning to previous resting status, an electrical signal is emitted from nuclei that is detectable by the scanner and allows reconstruction of static anatomic images.

Functional MRI (fMRI) is a variant of structural MRI. The primary difference, however, is that the dependent variable of interest in fMRI is the change in intensity of electrical signal emissions related to increases in blood flow (that are presumably caused by changes in neural activity). Thus, the focus of fMRI is on regional changes in brain activity rather than anatomic structure alone. As with O-15 PET, during fMRI specific stimuli or tasks are presented to the individual within the scanner in an attempt to elicit or increase brain activity. When neural activity increases in a brain region, there is a corresponding increase in blood flow to that region. In fact, this blood flow may increase by over 50 percent (58), beyond metabolic needs. This excess of flow to the region results in a localized surplus of oxyhemoglobin relative to deoxyhemoglobin in the cerebral venous and capillary beds. Oxyhemoglobin is naturally diamagnetic, while deoxyhemoglobin is paramagnetic (i.e., becomes readily magnetized within a magnetic field). With increased neural activity and concomitant increased blood flow, there is a net increase in diamagnetic material (oxyhemoglobin), and a net decrease in paramagnetic material (deoxyhemoglobin). This results in an increased signal intensity that can be detected externally, and is represented as higher signal intensity on T2\* (“T2-star”) weighted scans. This change in signal intensity is referred to as the blood oxygen level dependent—or “BOLD”—effect (59).

As compared with other neuroimaging techniques, fMRI utilizes the body’s natural physical responses to high-strength magnetism, thus no exogenous radioisotopes or contrast agents are required. Anatomic resolution of fMRI is also superior to that of SPECT or PET. In addition, there are numerous activation paradigms that can be carried out in fMRI, and it allows for greater flexibility in paradigm with reference to repeatability and brevity of the overall scanning session in comparison to other techniques (2).

As with any imaging procedure, however, fMRI can be impacted by numerous variables, particularly in clinical populations such as TBI. Consideration must be made for head movement, normal high frequency noise within the scanner, morphologic brain abnormalities (e.g., frontal or temporal lobe resection secondary to trauma), claustrophobia, anxiety, boredom, or actual onset of sleep while in the scanner.

Although most contemporary MRI scanners can be adapted to perform fMRI, this technique is still investigational in most clinical populations, including brain injury (1). Thus, fMRI is primarily a research tool at this time and its availability is generally limited to academic medical centers. A single fMRI session generates a large volume of data, which necessitates considerations for computer hardware, data storage and data security. At present, fMRI protocols do not actually “automatically” or “objectively” yield brain maps, nor are there normative values for fMRI scans or activity levels. Resulting images

must therefore be carefully and skillfully reconstructed, and this reconstruction process should be considered as much of an art as science. The approach that one takes in reconstructing and displaying the data in the form of brain images data will impact the display, and potentially the interpretation, of the end product.

## FMRI STUDIES OF BRAIN INJURY

At the time of this writing, there are very few fMRI studies of individuals with TBI, although there are several centers with active funding and ongoing protocols that will address this significant dearth in the scientific and clinical literature.

In the first fMRI studies of individuals with TBI (60–61), the investigators examined individuals with a very recent history of mild brain injury (i.e., within the previous 30 days). The individuals with mild TBI demonstrated intact behavioral performance on a verbal working memory task, but they did show right hemisphere lateralized fMRI activation in response to increased working memory load, as compared to healthy controls. In subsequent fMRI investigations of working memory following moderate and severe TBI (62–63), increased blood flow and more widespread dispersion of cortical activation was noted during working memory tasks. This again suggests that increased cognitive effort is reflected in increased brain activation on fMRI. In a study of working memory and response inhibition, fMRI was used to demonstrate increased recruitment of cerebral resources following severe diffuse TBI, particularly during response inhibition or when task difficulty was increased (64). This greater expenditure of effort to achieve overtly normal behavioral performance has also been demonstrated in an fMRI study of simple psychomotor execution (i.e., finger-tapping) among individuals with TBI examined several years after injury (65). One recent case study (66) has demonstrated correlations between changes in fMRI activations and improvement in cognitive status following rehabilitation of an individual with severe TBI, a compelling finding that warrants replication.

Although fMRI represents a very advanced approach to brain imaging vis-à-vis cognitive functioning when compared to SPECT or PET, it has not reached a sufficient threshold of evidence for routine use at any level of injury severity after head trauma. Given the paucity of fMRI research in TBI, the ACR has not fully evaluated fMRI and continues to classify this procedure as investigational in the examination of any level brain injury.

## FUTURE RESEARCH

The past few years have seen tremendous advances in functional neuroimaging technologies and approaches to

data analysis. In addition, there have been exploratory studies in several clinical populations, including TBI. In spite of these advances, these techniques remain investigational in most clinical applications (67). As with any technology, the transition from “investigational” to “routine” will not occur overnight, nor will it occur solely from the publication of a handful of case studies or small investigations drawn only from highly selected cases. It will occur after much additional, well-designed, systematic research (68). This should not be misinterpreted as a fatalistic statement, however. It is, in fact, the expectation of the authors that functional neuroimaging technologies will eventually demonstrate sufficient sensitivity and specificity to warrant routine clinical application, particularly among individuals with much potential to be helped by rehabilitation.

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# 13

## Electrophysiologic Assessment Techniques: Evoked Potentials and Electroencephalography

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**V**arious behavioral measures have been used to identify cognitive deficits as well as to predict functional outcome in traumatic brain injury (TBI). However, results among these studies have often conflicted (1, 2). Recently, advances in computer technology have facilitated electrophysiologic data acquisition and faster processing speed. As a result, electrophysiologic techniques have resurfaced as potentially powerful clinical measurements. As clinicians, we encounter persons with a variety of lesions in the nervous system. We are often expected to establish early diagnosis and treatment, as well as to provide continued monitoring of the recovery process. In this chapter, we summarize the potential applications of somatosensory evoked potentials (SEPs), brainstem auditory evoked potentials (BAEPs), conventional electroencephalography (EEG), P50, and P300 as objective measures in evaluating cognitive function, as well as their efficacy in predicting outcome in persons with TBI.

### **SOMATOSENSORY EVOKED POTENTIALS**

The evoked potential (EP) is an electrophysiologic response of the nervous system that occurs as a result of repeated sensory stimulation (3). Different from conventional EEG,

which shows continuously varying brain activity, EPs are averaged responses, which are temporally related to the incoming stimuli (4). Many EP measurements have been tested for their efficacy in clinical evaluation and in predicting functional outcome (5–7). Some tests provide reliable prediction of ominous outcomes (8, 9), while others prognosticate favorable outcomes (6, 7). SEPs seemed to belong to the former category (6, 9–13).

SEPs are responses of the nervous system to various sensory stimuli, including electrical, tactile, vibration, or painful stimulation. Among these stimuli, electrical stimulation has been most popular due to its ease of use. Short-latency SEP (SSEP) is a part of the SEP occurring within 50 msec after peripheral nerve stimulation in either upper or lower extremities (14). SSEPs are relatively independent from level of consciousness, while middle or long latency SEPs are influenced by cognitive status to a larger degree. Due to its reliability and stability, SSEP is commonly used for clinical evaluation and prognostication in TBI (4, 10). An example of normal SSEP from stimulation of median nerve is illustrated in Figure 13-1.

For traumatic coma in adults and adolescents, bilaterally absent cortical SEP responses predicted a 95 percent probability of non-awakening from coma (10, 15). Beca and colleagues studied SEPs within 4 days of coma onset in children with severe brain injury (16), and found that

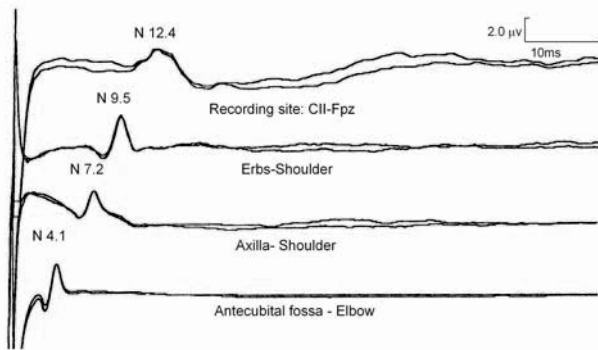


FIGURE 13-1

Normal SSEP waveforms from stimulation of left median nerve at the wrist

absent SEPs had very high positive predictive values (92–100 percent) for unfavorable outcome. In children with TBI, the likelihood of awakening from coma despite bilaterally absent SEP response was approximately 7 percent (10, 15). In a recent study by Lew et al. (6), bilateral absence of cortically recorded median nerve SEP within 8 days of severe TBI (Glasgow Coma Scale  $\leq$  8) was strongly predictive ( $p < 0.005$ ) of the worst functional outcome, namely, death or persistent vegetative state. In the above study, specificity and positive predictive values of absent SEP response for death or persistent vegetative state were as high as 100 percent at 6 months post-TBI.

In addition to SEP, there have been efforts to combine other evoked potential studies using so called “multimodality evoked potentials.” Shin et al. performed BAEP and SEP in TBI patients, and compared the results with clinical outcome (11). Although neither of the electrophysiologic measurements showed significant correlation with the cognitive level at a one-year follow-up, SEP increased the predictive value of initial clinical parameters including Rancho Los Amigos Scale or age. As for visual evoked potential (VEP), it has been utilized independently to evaluate visual impairment such as post-traumatic vision syndrome after brain injury (17, 18).

Several factors must be taken into consideration during the interpretation and analysis of the SEP waveform. For example, peripheral neuropathy of the nerve being stimulated may prolong the latency of cortically recorded potentials. Evoked responses recorded from the brainstem and cervical spine should be reviewed to rule out concurrent spinal cord injury. To distinguish central pathology from peripheral pathology, central conduction time (from the brainstem or Erb’s point to the cortical level) can be used (19). Increased level of sedation may reduce the amplitude of cortical SEP. Therefore, when the SEP amplitude is too small, it is prudent to repeat the test after removal of sedation (10). All things considered, decisions regarding continuation of life support should not depend totally upon SEP testing, but instead rely on overall

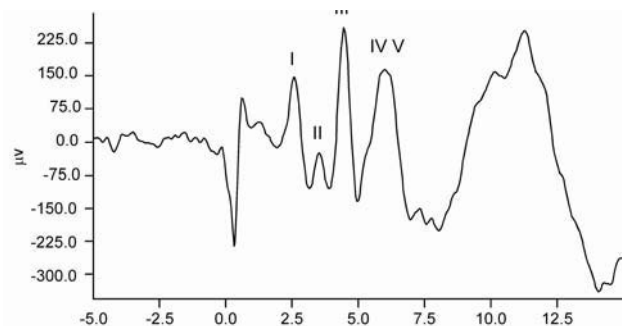


FIGURE 13-2

Normal brainstem auditory evoked potential waveform

clinical status, together with other laboratory findings and, most of all, family input.

### BRAINSTEM AUDITORY EVOKED POTENTIALS

Brainstem Auditory Evoked Potentials (BAEPs, also known as BAER, brainstem auditory evoked response) represent the electrophysiologic response of the central nervous system to repeated click stimuli, and is characterized by a pattern of 5 neurogenic waves (20). The BAEP wave I originates from the cochlear nerve, and wave II arises from the cochlear nucleus. Waves III, IV, and V originate from the superior olivary complex, lateral lemniscus, and inferior colliculus, respectively. An example of normal BAEP waveform is illustrated in Figure 13-2.

Prolongations of interpeak intervals between I–III, III–V, or I–V have been reported in patients with TBI, (11, 21–24). The most ominous finding is complete absence of a repeatable waveform. In a study on comatose children and adolescents with traumatic brain injury, BAEP abnormality was found to be about 40 percent of the 62 patients tested (25). In a meta-analysis, it was concluded that normal BAEP obtained within the first week of TBI onset had a very good prognostic value for awakening from coma (26), while EEG did not have much clinical utility. However, another independent study showed that the presence of BAEP in post-coma unawareness patients did not have any significant prognostic value, because the presence of normal BAEP in these patients may merely suggest that the brainstem had been spared despite significant injury above the brainstem (27).

In mild TBI, prolongation of BAEP wave I and III latencies had been observed soon after concussion, and prolongation of BAEP interpeak intervals (between wave I and V) had been noted from the first day of TBI (28). In other studies of persistent post-concussion syndrome, no significant BAEP latency delays were found (29). In more severe cases of TBI, prolonged interpeak interval persisted for several weeks (28, 30, 31). It should also be

noted that when more rigorous normative values were applied (abnormality defined as greater than 2.5 SD, rather than 2.0 SD, from the mean), no abnormalities in BAEP were noted after mild TBI (32). Also, in a group of amateur boxers ( $N = 47$ ) who supposedly had repeated concussions, no differences in BAEP results were observed when compared to other athletes with low risk of TBI (33). There have been several studies on BAEP to determine its correlation with dizziness. In patients with post-concussion syndrome, the BAEP alterations were not associated with dizziness or abnormal vestibular function (34). In another study involving patients with mild head injury, significantly prolonged BAEP latency was observed. However it was not correlated with outcome after 3 months (35).

The value of BAEP for hearing screening has already been established in newborns because of its objective nature and ease of use (36, 37). Due to co-existing cognitive problems, it is sometimes difficult to detect hearing dysfunction in TBI patients, especially in the early stages of recovery (38). This may result in delays in audiological, surgical, and rehabilitative interventions. Review of literature from 1975 to 2001 showed that the incidence of hearing problems for various degrees of TBI varied from 7 to 50 percent (25, 39–43). A recent review of inpatient records from a TBI unit showed that 17 percent of moderate to severe TBI patients showed abnormal behavioral audiograms after the injury (44). If hearing screenings with BAEP were performed prospectively on all moderate-to-severe TBI patients, the incidence could be higher than 17 percent. In a study on 40 TBI patients (22), BAEP results were compared with behavioral audiometry, and the authors concluded that BAEP was more diagnostic than pure tone audiometry in the evaluation of brainstem dysfunction. In conclusion, the utility of BAEP in TBI may be limited to evaluation of brainstem dysfunction and hearing impairment (45).

## ELECTROENCEPHALOGRAM

Conventional electroencephalogram (EEG) measures electrical activity generated by the brain via surface electrode recording. An example of ongoing EEG is illustrated in Figure 13-3. Traditional EEG studies typically involve subjective and qualitative analysis, although efforts are being made to objectively quantify the EEG data, such as Fourier Transform (FT) of the frequency bands. With advances in computer-based signal processing technology, quantitative EEG (QEEG) analyses may gain wider use in evaluating TBI patients (46).

### Conventional EEG

There are four basic components in EEG waveforms. Alpha waves (8–12 Hz) are seen in the awake but relaxed

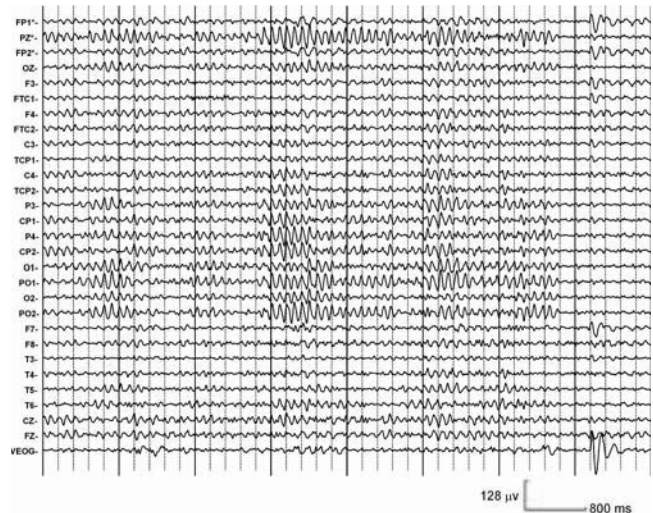


FIGURE 13-3

Continuous electroencephalography recording by surface electrodes

state, while beta waves (12–30 Hz) are observed in the fully awake state. Delta waves are the slowest waves (less than 4 Hz), which are related to nondreaming deep sleep. Theta waves (4–8 Hz) also are associated with hypnotic or meditation states of consciousness. These waves are affected by age and recording sites. The pathologic brain wave patterns include focal or generalized spikes observed in patients with convulsive disorders. Other pathologic patterns vary from overall slowing to altered proportion of waves. Burst suppression pattern is characteristically seen during the induction stage of anesthesia. It is typically shown as a mixed pattern of high-voltage bursts and low-voltage suppression period, which are also related to anoxia, coma, and brain damage (47, 48).

EEG patterns have been empirically used to assess the severity of TBI and to predict their functional outcome (49). In 1973, Bricolo (49) reported that EEG is a useful evaluation tool for comatose TBI patients. They found that subjects with “spindle patterns” had relatively favorable prognosis, and patients with monophasic or slow disorganized electric activity patterns without response to environmental stimuli had much higher mortality rate. Synek (50) studied the EEG patterns of patients with cerebral anoxia or head injury, and concluded that those who responded to external stimuli were usually associated with good outcomes. Some other favorable EEG patterns included normal activity, rhythmic theta activity, frontal rhythmic delta activity, and spindle pattern. On the other hand, epileptiform activity, nonreactive, low-amplitude delta activity, and burst suppression patterns with interruptions of isoelectricity were associated with poor prognosis. Needless to say, patients with complete isoelectric EEG activity had the highest mortality.



Although EEG analyses may provide some prognostic information for patients with severe TBI, there are issues with their application in mild TBI. Jacome et al. (51) found no EEG abnormality in 24-hour ambulatory EEG monitoring of mild TBI patients. One and a half decades later, Voller et al. (52) did a combined EEG/MRI study. Again, no EEG abnormalities were observed in mild TBI patients. Even in patients with structural lesion per MRI, no focal change in EEG was noted. Based on the aforementioned studies, conventional EEG analysis is not highly regarded as either a diagnostic or prognostic tool in evaluating the patients with mild TBI.

### Quantitative Electroencephalography

Quantitative electroencephalography (QEEG) is based on highly sophisticated computation of EEG signals. The fundamental element of QEEG is spectral analysis, which decomposes the complex EEG signal into various component frequencies. The amount of alpha (8–12 Hz), beta (12–30 Hz), delta (0–4 Hz), and theta (4–8 Hz) component activity contained in the EEG signals are quantitatively isolated and stored in digitized format for further analysis. Topographical mapping of different frequency bands (sometimes referred to as BEAM, brain electrical activity mapping) can be made based on the results of spectral analyses. QEEG has clinical value in certain neurologic abnormalities such as epilepsy, cerebrovascular disease, and dementia (53). However, experts in neurophysiology have not completely reached their consensus regarding the clinical utility of QEEG in mild head injury, moderate head injury, or post-concussion syndrome (53–56).

Due to the availability of digital recording and computer-based real-time quantitative analyses, many researchers have devoted their time and efforts to exploring QEEG as a tool for evaluating TBI patients. Bricolo et al. (57) first studied comatose TBI patients by spectral EEG analysis. They suggested that interhemispheric frequency band asymmetries were associated with poor outcome. In contrast, patients with spontaneous EEG power spectrum variability and persistence or return of EEG activity within the alpha or theta frequency were correlated with favorable prognosis. (58, 59).

Comparing the predictive values between QEEG and Glasgow Coma Scale (GCS) in severe TBI patients, Karnaze et al. (60) showed that altered spectral patterns were correlated with better survival, and its predictive value was equivalent to, but not significantly higher than that of GCS. Thatcher et al. (61) compared QEEG, GCS, brainstem auditory evoked potential (BAEP), and Computed Tomography (CT) in outcome prediction of 162 comatose TBI patients. EEG phase pattern was demonstrated to be the most prognostic, followed by EEG coherence, GCS, and brain CT, respectively. Alster et al. (62)

also demonstrated that spectral EEG analyses were more predictive of brain injury outcomes than GCS and BAEPs.

Thatcher et al. (63) compared QEEG patterns between patients with mild TBI and age-matched controls. An overall classification accuracy of 94.8 percent was reported. Mild TBI subjects showed increased coherence and reduced phase in frontal and temporal areas, decreased alpha band amplitudes in the parieto-occipital territories, and reduced spectral power difference across anterior/posterior cortical regions. Tebano (64) also performed spectral EEG analysis in persons with brain injury. Their results showed that mild TBI patients had a shift in peak alpha frequency band toward lower frequency values. Twelve years later, Cudmore (65) also demonstrated that EEG coherence pattern differentiated controls from patients with mild TBI. Increased alpha/theta ratio was observed in mild TBI patients (66), possibly due to reduced theta activity, with relatively stable alpha activities.

In summary, these studies imply that QEEG findings may be better than conventional EEG in studying mild TBI patients. However, inter-research comparison and meta-analysis are problematic due to lack of standardized techniques and inconsistent inclusion/exclusion criteria. In addition, QEEG analyses are derived from vast amount of data points over various recording electrodes, and researchers typically use multiple analyses to derive the results. Consequently, type I error is a major concern, and multiple inter-electrode comparisons may yield some “statistically significant” but not “clinically meaningful” results.

### PAIN-RELATED POTENTIAL (P250)

Deep brain stimulation (DBS) of various brain regions (e.g., mesencephalic reticular formation or the thalamic center median-parafascicular (CM-Pf) complex) has been used to evaluate or even promote recovery from the persistent vegetative state (PVS). To monitor clinical utility of DBS, the late positive wave of cortical potentials elicited by painful stimuli (pain-related potential, P250) has been investigated (67–69). In chronic vegetative state, the depressed P250 was temporarily enhanced by DBS. A persistent enhancement of the P250 was also correlated with better clinical outcome (67). The P250 may provide objective and quantitative information regarding the level of cortical responsiveness to painful stimuli in persons in low level neurological states following brain injury.

### P50

The P50-evoked response is the event-related potential (ERP) response around 50 msec to auditory stimuli (P50 ERP). This potential is recorded at the scalp, and reflects the cholinergically dependent, hippocampally mediated,

and pre-attentive process of sensory gating to auditory stimuli (70, 71). Traditionally, paired auditory stimuli are used for P50 study. The procedure is as follows: First, hearing threshold (in dB SPL) is determined, and the auditory stimuli are presented at 25–45 dB SPL above the hearing threshold (72). Employing the International 10–20 System of Electrode Placement (73), the P50 potential is recorded at Cz-A1 with a ground electrode at A2. Pairs of auditory stimuli (1 msec duration, 20Hz–12kHz) are presented with certain intra-pair (around 0.5 sec) and inter-stimulus (around 10 sec) interval. An overall grand average is obtained for both the conditioning and test P50 responses. The P50 latency and amplitude can be identified by computer algorithm (72, 74).

The P50 ratio (in percentage) is the amplitude ratio of the test P50 to the conditioning P50. Examples of P50 suppression and nonsuppression are illustrated in Figure 13-4. It is used as an index for auditory sensory gating (72). P50 suppression is defined as a P50 ratio of  $\leq 40$  percent, and P50 nonsuppression is  $\geq 60$  percent. P50 ratio between 40 and 60 is considered as an indeterminate P50 suppression (72). Arciniegas et al. reported that the P50 ratio was significantly increased in TBI (75). Interestingly, the P50 ratios of different TBI subgroups, categorized by duration of post-traumatic amnesia (PTA) did not show significant difference from one another. Those TBI subjects with similar level of cognitive impairment at the time of testing demonstrated similar amount of abnormal P50 suppression despite varying severity of initial brain injury. In another study (72), the frequency of P50 nonsuppression was investigated in patients with persistent posttraumatic attention and/or memory impairment. Preliminary analysis showed that the majority of TBI subjects have discernable P50 response, and that P50 nonsuppression is common among TBI patients with subjective symptoms of attention and memory

impairments, providing some evidence that clinically impaired auditory gating is variably correlated with P50 nonsuppression.

Regarding the source of P50 potential, it has been suggested that the generator is located at the hippocampus (74, 76, 77). Sensory gating process may facilitate stimulus selection and information processing, which are important for attention and memory function (72). It was suggested that impaired sensory gating cause attention and memory impairments after TBI (78), and that abnormal P50 findings may be a useful marker for cholinergic dysfunction (72, 75, 79, 80). In summary, these studies suggest that the P50 response may be useful not only for evaluating cognitive dysfunction, but also for monitoring pharmacological interventions in TBI.

### EVENT-RELATED POTENTIALS/P300

Event-related potentials (ERPs) are cognitive potentials recorded over the scalp. They have been regarded by psychophysicists as indicators of information processing, which may not be fully appreciated by measuring behavioral performance alone (6, 81, 82). In the active ERP paradigm, the subject is asked to discriminate a rare/target stimulus (typically with occurrence rate of 20 percent) from an interrupted series of frequent/nontarget stimuli (80 percent occurrence rate) (83). When averaged appropriately, the target stimuli generate a prominent positive peak (P300) approximately 300 msec after stimulus onset (83–85). The P300 response reflects active attention, working memory, and the ability to detect novel stimuli among a series of similar signals (81, 84, 86, 87). Amplitude of P300 reflects the amount of cerebral activity required to process information and maintain working memory as the controlled environment is updated with incoming sensory input (86). Studies have shown that the P300 latency is a reliable indicator of stimulus classification speed, which is independent from the response selection processes (88, 89). Traditionally, simple auditory and visual tasks such as tone and color recognition have been widely employed in ERP testing due to its ease of use (83, 86, 90, 91). Although these tasks are rather primitive when compared with other paradigms (e.g., word recognition, affect recognition), simpler tasks have the advantage of generating larger amplitudes and shorter latencies, which in turn simplify the data analysis process. An example of normal auditory P300 response is shown in Figure 13-5. The waveform was recorded at an Cz electrode, using an active oddball paradigm with pure tones as stimuli.

Not surprisingly, P300/ERP studies have been applied to patients with cognitive impairments (92) and psychiatric disorders (93, 94). For comatose patients who are unable to participate actively in the testing process, the passive ERP paradigm can be used (6, 95–98). Several brain

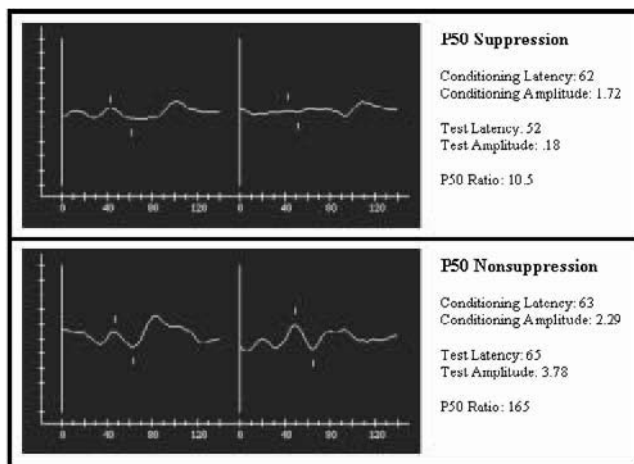
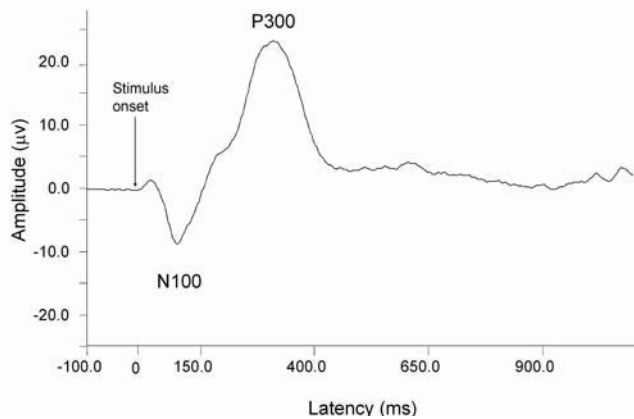


FIGURE 13-4

P50 suppression and nonsuppression (72)



**FIGURE 13-5**

Normal auditory event-related potential (ERP) waveforms from pure tone (1000 Hz versus 500 Hz) discrimination task

injury studies utilized simple tones as stimuli (7, 95–99), which yielded P300 responses in about 30 percent of apparently comatose patients. Preserved P300 seemed to predict the emergence from coma (95, 99, 100) and higher chance of recovery (90 percent or higher) in long-term follow-up (95, 99, 101). However, the absence of P300 did not exclusively prognosticate ominous outcome (6).

Based on recent data published by various researchers (6, 101, 102), it was apparent that preserved P300 component was associated with good clinical outcomes, while it was coincidentally noted that the N100 component also correlated with favorable outcome. In one study (101), investigators recorded auditory P300 potentials using three different passive paradigms both in normal subjects and in patients with severe consciousness impairment after TBI. Results showed that the N100 latency was longer, with significantly depressed amplitude in TBI patients than in normal subjects. It suggested that cognitive processing of exogenous sensory stimuli may still take place, albeit with some delay, when the patients' level of consciousness appeared to be severely impaired. Although the N100 response was thought to be associated with passive perception of incoming sound (103), there is evidence to suggest its involvement with alertness and stimulus processing (81). Based on the above-mentioned studies, it is possible that both the N100 and P300 components are associated with active information processing (101, 102, 104).

To increase the ecologic validity of the ERP task, recent studies employed speech stimuli such as patients' names (6, 101, 105). From a theoretical standpoint, a person's own name would generate a more robust ERP response. By comparing three different speech targets (subject's own name, the word "mommy," and a meaningless speech sound), a recent study demonstrated that the subject's name was indeed a viable target for eliciting cognitive ERP (102).

ERP testing has also been used to monitor effects of caffeine, nicotine, alcohol intake, and various psychostimulants. Caffeine and nicotine increased the P300 amplitude and shortened the latency, while acute alcohol consumption decreased the amplitude and prolonged the latency (81). Anderer et al. compared the pharmacologic effects of various drugs in healthy subjects. While methylphenidate and citalopram enhanced P300 in various cortical regions, lorazepam and haloperidol depressed P300 component (106). From a theoretical perspective, ERP might be a useful tool in evaluating the pharmacologic effect of various so called "cognitive enhancers" after brain injury.

In summary, ERP may be valuable in investigating residual cognitive function of patients with TBI because of its noninvasive nature (107) and superior temporal resolution (108). Also, using multi-channel recording, ERP may contribute to localization of certain brain activities based on dipole theory. With advances in computer technology, ERP may complement behavioral testing in the comprehensive evaluation of cognitive function.

## CONCLUSION

So far, we have discussed use of various electrophysiologic measurements for persons with TBI. SEP is a reliable prognosticator for ominous outcome after severe TBI. Combining ERP with SEP increases the power for predicting a favorable outcome. P300 and P50 are valuable in evaluating pharmacological effects of various drugs on cognitive function. The utility of BAEP in TBI is limited to evaluation of brainstem dysfunction and hearing impairment, rather than actual cognitive function. Although conventional EEG and QEEG have their inherent limitations, they may gain wider use as technology improves and more standardized studies are performed.

Neuro-imaging studies, such as MRI (magnetic resonance imaging) or fMRI (functional MRI) have been used to obtain structural information along with electrophysiologic information (109–112). While ERP measurement can provide high temporal resolution for evaluation of cognitive processing, fMRI detects regional changes of brain activity in response to specific task performance. However, most of these combination studies (using imaging and electrophysiologic measurements) have been performed on psychiatric patients, and have been rarely applied to persons with TBI. As for future research, the addition of electrophysiologic and neuro-imaging studies may provide comprehensive, objective, and valid assessments of cognitive status in persons with TBI, and may be useful in prognostication of long-term functional outcome.

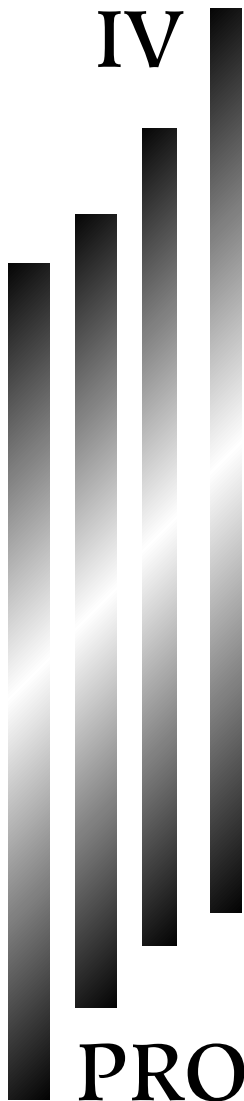
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**PROGNOSIS AND  
OUTCOME**



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# 14

## Prognosis After Severe TBI: A Practical, Evidence-Based Approach

*Sunil Kothari*

*It seems to be highly desirable that a physician should pay much attention to prognosis. If he is able to tell his patients when he visits them not only about their past and present symptoms, but also to tell them what is going to happen, as well as to fill in the details they have omitted, he will increase his reputation as a medical practitioner and people will have no qualms in putting themselves under his care.*

*Hippocrates*

Like diagnosis and treatment, prognosis is a fundamental responsibility of all clinicians. This is especially true after a traumatic brain injury, when uncertainty about the future compounds the suffering already experienced by patients and families. Indeed, families have identified information about prognosis as one of their most important needs in the aftermath of a traumatic brain injury (1–3). Unfortunately, this need often goes unmet, as families report they were rarely provided adequate prognostic information (2,3).

Providing patients and families with this information can help in several ways. Knowing what the future might hold allows families to gain some cognitive control over a situation they otherwise feel powerless to affect. Moreover, there is a symbolic importance to prognosis: patients and families want to believe their condition is

understood (4). Simply knowing that the clinician understands their condition can alleviate anxiety. Given the importance of prognosis for patients and families, some authors have even suggested that prognostication is an ethical *duty* for clinicians (4).

Despite its clear importance, clinicians often neglect prognosis. Some reasons for this neglect apply only to the delivery of *poor* prognoses: a lack of training in the delivery of “bad news”, the emotionally demanding nature of providing a poor prognosis, a fear of extinguishing hope, and the fact that a poor prognosis highlights the limits of professional help (4). Other barriers can affect *any* act of prognosis: the belief that prognostication is arrogant or hubristic, a lack of facility in probabilistic reasoning, and the difficulty in extracting clinical guidelines from a large body of literature (4).

Because of this difficulty in developing guidelines based on the research literature, health care professionals often rely on their own clinical experiences in formulating prognoses. However, such an approach is of limited value: not only is a clinician’s personal experience subject to selection bias, it is also prone to significant cognitive distortion (5,6). Many studies have shown that a clinician’s “subjective” estimation of prognoses is often far less accurate than those derived from well designed studies (7–9).

Yet, providing prognostic information based on these studies can be difficult for TBI professionals. The

literature is vast, with hundreds of studies reported, all varying in focus, design, and quality. Also, most of the studies were designed or reported in a way that makes it difficult to derive *clinically* useful guidelines. Often, they report only general associations (e.g., “outcome is related to the length of coma”). Even when these associations are quantified, it is done in a way that limits their applicability to individual cases (for instance, by using regression equations).

The purpose of this chapter is to address these obstacles and thereby derive accurate and useful guidelines from the relevant literature. It is hoped that this information will enable TBI professionals to make the most accurate prognoses possible, both to inform their own clinical decisions as well as to provide the desired information to patients and families. Of course, other reviews of this topic exist (10–24), including several excellent ones that have recently been published (25, 26). The review presented here differs from the others in three important ways. First, an attempt was made to review *all* available and relevant studies. Second, this is the first review to apply an evidence-based approach to this area. Finally, the primary aim was to develop guidelines that will be *clinically* useful.

The chapter is divided into five major sections:

- a summary of findings
- guidelines for communicating prognostic information
- a brief review of recent developments in the field
- an appendix on guidelines for evaluating studies on prognosis
- an appendix describing the methodology of the literature review

The core of the chapter is contained in the next two sections, which summarize the findings of the evidence-based review and provide guidelines on communicating this information to patients and families. The third section briefly describes developments in the area which will likely assume greater importance over the next several years. The first appendix provides a guide for evaluating future studies on prognosis. The second appendix provides a detailed description and justification for the methodology guiding this review. To maximize the usefulness of this chapter as a future reference, all the important information is summarized in the figures and tables. Therefore, after an initial reading of the entire chapter, readers can then simply refer to the tables and figures to review the essential information. This chapter does not address topics relevant to prognosis after TBI that are covered elsewhere in the textbook (see Figure 14-1).

## SUMMARY OF FINDINGS

*Medicine is a science of uncertainty and an art of probability.*

*William Osler*

Prognosis in Pediatric TBI - Chapter 20 Prognosis in Vegetative State - Chapter 25 Prognostic Value of Electrophysiological Measures – Chapter 13 Outcome Measures Used in Prognosis Studies – Chapter 16 Late Predictors of Return to Work - Chapter 61 Prognosis after Mild TBI - Chapter 22–23 Prognosis of Life Expectancy - Chapter 17
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FIGURE 14-1

*Topics Relevant to Prognosis Covered Elsewhere*

### Clinical Utility: The Concept of a “Threshold Value”

The primary purpose of this chapter is to provide clinicians with information that is not only evidence-based but also *practical*. The nature of the studies in this area makes this difficult, for several reasons. First, most of the relevant studies do not *directly* address issues of prognosis. Instead, they often have simpler aims, such as providing a description of the possible outcomes after TBI as well as the factors associated with these outcomes. As a result, the findings are reported in such a way that only the broadest generalizations are possible (e.g., that the initial Glasgow Coma Scale (GCS) score is correlated with outcome after a TBI). Although this knowledge does represent an advance in our understanding of TBI, it does little to help clinicians who are trying to prognosticate for individual patients. Even when these associations are quantified, it is in a form that is not clinically useful (e.g., as correlation coefficients).

This was a limitation even of those studies that directly addressed prognosis. For example, the relationship between a potential predictor variable and an outcome might be expressed as a path coefficient or the percentage of variance explained. Yet, both clinicians and laypeople are more used to thinking about, for instance, probabilities (e.g., “what are the chances that he will ever work again?”). Unfortunately, there is no straightforward way to translate results expressed as path coefficients,  $R^2$ , log-likelihood’s, correlation matrices, etc., into prognoses that are meaningful to the clinician, let alone the family. For most clinicians, our knowledge begins and ends simply with the awareness that certain variables are associated with outcome (e.g., GCS, pupillary abnormalities, etc.), without knowing how to apply that information to individual cases. There were a handful of studies that actually did provide practical guidelines for clinicians (e.g., by using simple formulas, prediction trees, or scores from specially designed scales), but they did not meet the other inclusion criteria of this review.

To maximize the clinical utility of studies that did meet the inclusion criteria, the results were interpreted

through the use of threshold values. These are values of a predictor variable above or below which a particular outcome was especially unlikely. For example, several studies reported that no one with a duration of PTA over three months achieved a good recovery as defined by the Glasgow Outcome Scale (GOS) (Figure 14-2). Thus, three months would be considered a threshold value for the duration of PTA, at least in terms of excluding the possibility of a good recovery on the GOS (Figure 14-3). Conversely, several studies found that no one who had a duration of PTA of *less than* two months ended up severely disabled (by GOS criteria); two months would then be the threshold value for excluding the possibility of severe disability.

As “milestones” in a patient’s recovery, threshold values can be useful to clinicians. For instance, as the length of a patient’s PTA extends beyond three months, rehabilitation clinicians can counsel family members about realistic expectations for the future. On the other hand, if two months have not yet elapsed since the injury, clinicians can give hope to families even if the patient is still in PTA.

Studies that reported their results in a way that allowed the determination of threshold values were especially important for this review. Unfortunately, less than a third of the included studies did so. In some cases this

was because the variable in question did not turn out to have a threshold value. This occurred when, regardless of the score or value, a prognostic factor was associated with all possible outcomes. For instance, for any initial GCS value between 3 through 8, all the outcomes on the GOS are possible, so there are no threshold values for this variable. With other factors, such as PTA, it does make sense to speak of threshold values. Even in these cases, however, only a minority of the studies were designed or reported so that one could determine what those threshold values actually were. The guidelines in this chapter relied heavily on these few studies, since they were the ones that provided the most useful information for clinicians.

Because of the limited number of studies involved, it was important to provide independent verification of the validity of their conclusions. This was done by determining if the results were consistent with the findings of the other, excluded, studies. For example, excluded studies were reviewed to determine if any of them reported a significant number of cases of good recovery on the GOS when the duration of PTA extended beyond three months (one of the threshold values derived from the included studies). If the excluded studies also converged on the same threshold values, one could be more sure of the validity of the original values. In fact, the results of the excluded studies were consistent with almost all the derived threshold values; the few exceptions were not clinically significant and are discussed in more detail below (in the sections on individual predictor variables).

The threshold values that were chosen were those that allowed one to exclude either a good recovery on the one hand or a severe disability on the other; no attempt was made to determine similar threshold values for moderate disability. This was motivated by the belief that, for most family members, it is the GOS categories of severe disability and good recovery that are of most interest in the subacute period. Families want to know how long they can still hope for a good recovery (and may not be as concerned, during that time, about whether the alternative is moderate disability or severe disability). Conversely, it is reassuring to families to hear it is unlikely the patient will be severely disabled (even if neither they nor the clinician knows whether the eventual outcome will be a good recovery or moderate disability).

Of course, interpreting threshold values is not unproblematic. There is a degree of statistical uncertainty for all calculated threshold values. For example, even if no one with a duration of PTA greater than three months had a good recovery in a particular study, such an outcome is still *statistically* possible. This statistical uncertainty can be quantified using confidence intervals. The lower end of the confidence interval would be zero (in a study where no one had the outcome of interest), while the upper end would represent the largest number of people who could have had the outcome of interest. The use

- DEAD
- VEGETATIVE STATE (“alive but unconscious”)
- SEVERE DISABILITY (“conscious but dependent”)—unable to live alone for more than 24 hours: the daily assistance of another person at home is essential as a result of physical and/or cognitive impairments.
- MODERATE DISABILITY (“independent but disabled”)—independent at home; able to utilize public transportation; able to work in a supported environment.
- GOOD RECOVERY (“mild to no residual deficits”)—capacity to resume normal occupational and social activities, although there may be minor residual physical or mental deficits.

**FIGURE 14-2**

*Glasgow Outcome Scale*

A value of a predictor variable above or below which a certain outcome is especially likely or unlikely.  
 Example: *If post-traumatic amnesia (PTA) lasts more than three months, a person is very unlikely to achieve a “good recovery” on the Glasgow Outcome Scale (GOS).*

**FIGURE 14-3**

*Definition of Threshold Value*

of confidence intervals in this context is further explained in the second appendix.

There were also instances where two or more studies differed in the threshold values they identified (for instance, excluding the possibility of a good recovery after a PTA of two months in one study but not until a PTA of three months in another). As discussed below, a decision was made to err on the side of conservatism in these situations by choosing the value (larger or smaller, depending on the outcome), which minimized the possibility of an inaccurately pessimistic prognosis. So, in this example, one would choose three months of PTA as the threshold value in order to avoid discounting the possibility of a good recovery in those patients whose PTA lasted between two to three months.

### Brief Comment on Methodology

The inclusion criteria are summarized in Figures 14-4 and 14-5. The second appendix provides a detailed review and justification for selecting these criteria. For present purposes, it is noted that the review focused on studies of adults who had sustained a moderate or severe TBI (either closed or penetrating). The predictor variables represented the information most likely to be available to rehabilitation clinicians: initial Glasgow Coma Scale score (GCS), length of coma, duration of post-traumatic amnesia (PTA), age, neuroimaging findings, and results of early neuropsychological testing. The outcomes of interest (assessed at 6 months or later) were vocational reentry, return to independent living, or the classification on the Glasgow Outcome Scale (GOS). The use of the GOS as the primary outcome of interest requires justification; this is provided in the second appendix.

Out of the hundreds of articles reviewed, there were only 35 studies that met all the inclusion criteria: 12 using neuroimaging predictors (27–38) (Table 14-1), 24 using clinical predictors (27, 29, 30, 33, 38–57) (Table 14-2), 2 focused on the elderly (58, 59) (Table 14-3), and 2 on

Outcomes studied should be relevant and meaningful to a layperson (e.g. family member) asking about prognosis.

Predictor variables should represent information easily accessible to rehabilitation clinicians.

The population studied should be similar to the population encountered by rehabilitation professionals.

The studies must meet minimal methodological criteria in terms of patient selection, follow-up, statistical analysis, etc.

**FIGURE 14-4**

*General Guidelines for Inclusion of Studies*

penetrating brain injury (60, 61) (Table 14-4) (the numbers add up to more than 35 because some studies investigated more than one prognostic factor). No studies that used early neuropsychological testing as a predictive variable met all the inclusion criteria. Neither did any studies that focused exclusively on moderate TBI. More importantly, of all the studies that were included, only a third allowed for the determination of threshold values. In particular, eight of the closed head injury studies reported threshold values with acceptable confidence intervals (0–12 percent): one for MRI, one for length of coma, two for length of PTA, and four for age. In what follows, the results of the studies are reviewed by predictor variable. The conclusions are summarized in Figure 14-6.

### MRI

*Summary* Two studies (32, 34) met the inclusion criteria, both using information from Magnetic Resonance Imaging (MRI) obtained within two weeks after injury. Both found the depth of the lesions correlated with outcome. Specifically, they discovered that lesions in the cortex or the white matter were not associated with worse outcome, whereas brain stem lesions were strongly associated with poor outcome. One study (34) also determined a

#### *Population*

1. Publication after 1983
2. Setting in North America, Western Europe, Australia, New Zealand, or Israel
3. Setting in either acute care or inpatient rehabilitation
4. Moderate and/or severe TBI (penetrating and/or closed)
5. Exclusively or primarily adult TBI

#### *Predictors*

6. Predictor variables: GCS (total), length of coma, PTA, age, neuroimaging (CT or MRI), and/or early neuropsychological testing.

#### *Outcomes*

7. Outcomes: GOS, vocational re-entry, and/or independent living
8. Outcomes assessed at 6 months or later

#### *Methodology*

9. Sample must represent consecutive admissions (whether done prospectively or retrospectively) or a random/neutral sampling of consecutive admissions
10. Sample size > 25
11. Follow-up greater than 80 percent
12. Statistical analysis performed (or, if not, enough information provided to analyze oneself)

**FIGURE 14-5**

*Inclusion Criteria for Studies Population*

**TABLE 14-1**  
**Neuroimaging**

STUDY	POPULATION	NUMBER	OUTCOME	PREDICTOR	FINDINGS ASSOCIATED WITH WORSE OUTCOME	STATISTICS	POTENTIAL "THRESHOLD" VALUES
Rao 1990	Inpatient rehab	79	Return to work (approx. 1.5 years)	CT (acute care)	Extent of CT damage (bilateral > unilateral > normal)	Univariate	None
Fearnside 1993	Severe; acute	315	GOS (6 months)	CT (admission)	Contusion, intracerebral hematoma & SAH	Multivariate	None
Kakariekka 1994	Severe; acute	414	GOS (6 months)	CT (admission)	Presence of SAH	Univariate & Multivariate	None
Walder 1995	Severe; acute	109	GOS (6 months)	CT (admission)	CT findings as characterized by Abbreviated Injury Scale and the Traumatic Coma Data Bank Classification	Univariate	None
Lobato 1997	Severe; acute	710	GOS (6 months)	CT (admission)	CT findings as characterized by Traumatic Coma Data Bank Classification	Univariate	None
Wedekind 1999	Severe; acute	57	GOS (> 6 months)	MRI (2 weeks)	Lesions in corpus callosum or basal ganglia or midbrain or total # of lesions	Univariate	None
Gomez 2000	Severe; acute	810	GOS (6 months)	CT (admission)	Status of cisterns, SAH, EDH, SDH, midline shift or contusion by univariate; status of cisterns, SAH, EDH & IVH by multivariate	Univariate & Multivariate	None
Firsching 2001	Severe; acute	102	GOS (2 years)	MRI (8 days)	Depth of lesion; (total # of lesions or corpus callosum lesions do not correlate w/outcome)	Univariate	No one with bilateral brainstem lesions achieved a good recovery (CI 0-8 percent)
Schaan 2001	All GCS (admitted to ICU); acute; isolated TBI	554	GOS (6 months)	CT (admission)	EDH, SDH, edema or contusion	Multivariate	None
Vos 2001	Severe; acute	63	GOS (6 months)	CT (admission)	CT findings as characterized by Traumatic Coma Data Bank Classification	Univariate	None
Mattioli 2003	All GCS (admitted to ICU); acute; included GSW	605	GOS (6 months)	CT (admission)	SAH	Multivariate	None
Rovlias 2004	Severe (isolated BI); acute	345	GOS (6 months)	CT (admission)	SAH; EDH; SDH	Multivariate	None

**TABLE 14-2**  
**Clinical Predictors**

STUDY	POPULATION/ AGE [RANGE (MEAN)]	NUMBER	OUTCOME	PREDICTOR	FINDINGS ASSOCIATED WITH WORSE OUTCOME	STATISTICS	POTENTIAL "THRESHOLD" VALUES
Born 1985	Severe; acute, 1-75 yo (23)	109	GOS (6 months)	Age	Older age	Univariate	None
Facco 1986	Severe; acute, 15-60 yo	56	GOS (6 months)	GCS; length of coma	Lower GCS	Univariate	None
Hans 1987	Severe; acute, 3-61 yo (23)	40	GOS (6 months)	Age; GCS	Older age; lower GCS	Univariate	None
Choi 1988	Severe; acute (30.8 yo)	523	GOS (6 months)	Age	Older age	Multivariate	None
Tate 1989	Severe; rehab, 15-45 yo (23.9)	100	GOS (6 years)	PTA; length of coma	Length of PTA; length of coma	Univariate	None
Narayan 1989	Severe; acute	133	GOS (>6 months)	Age; GCS	Older age; lower GCS	Multivariate	None
Rao 1990	Rehab, 17-66 yo (29)	79	Return to work (1 year)	Length of coma; age; PTA	Length of coma; older age; (length of PTA not correlated)	Univariate	None
Levin 1990	Severe; acute, 16-70 yo (27)	300	GOS (12 months)	GCS	Lower GCS	Univariate	None
Choi 1991	Severe; acute (30.9 yo)	617	GOS (12 months)	Age	Older age	Multivariate	None
Marshall 1991	Severe; acute (29.5 yo)	746	GOS (2 years)	GCS	Lower GCS	Univariate	None
Vollmer 1991	Severe; acute 15-80 yo	661	GOS (6 months)	Age	Older age	Univariate	No patient over 55 yo had a good recovery (CI 0-4 percent)
Bishara 1992	Severe; acute, 15-65 yo (25.7)	93	GOS (>6 months)	PTA; GCS; age	Length of PTA; lower GCS; (age not correlated)	Univariate and multivariate	No one had severe disability until PTA >2 months (CI 0-4 percent)
Godfrey 1993	Severe; acute (who survived acute care) 15-61 yo (25.38)	66	Return to work (>1 year)	PTA	Length of PTA	Univariate	None
Pennings 1993	Severe (GCS <5); acute, 20-92 yo	92	GOS (>6 months)	Age	Older age	Univariate	No patient over 60 yo had a good recovery (CI 0-7 percent)
Katz 1994	Rehab (with DAI), 8-89 yo	175	GOS (6 months)	GCS; PTA; Length of coma; age	Lower GCS, length of PTA, length of coma, older age (by univariate analysis); length of PTA, older age (by multivariate analysis)	Univariate and multivariate	No one with length of coma >2 weeks (CI 0-10 percent) or PTA >3 months (CI 0-11 percent) had a good recovery. Only 2 percent of patients with a PTA <2 months were severely disabled (CI .3-9 percent). Only 5 percent of length of coma <2 weeks were severely disabled (CI 2-12 percent)

**TABLE 14-2**  
*(continued)*

STUDY	POPULATION/ AGE [RANGE (MEAN)]	NUMBER	OUTCOME	PREDICTOR	FINDINGS ASSOCIATED WITH WORSE OUTCOME	STATISTICS	POTENTIAL "THRESHOLD" VALUES
Kakarieka 1994	Severe; acute 16–70 yo (36)	414	GOS (6 months)	Age	Older age	Multivariate	None
Walder 1995	Severe; acute 16–78 yo (26)	109	GOS (6 months)	Age	Older age	Univariate	None
Combes 1996	Severe; acute (38.5 yo)	198	GOS	Age	Older age	Multivariate	None
Ellenberg 1996	Severe; acute (that regained consciousness in acute care), 16- yo (29)	314	GOS (6 months)	PTA; length of coma; age	Length of PTA; length of coma; older age	Multivariate	None
Hawkins 1996	Rehab, 17–72 yo (27)	55	Return to work; independent living	GCS	None	Multivariate	None
Hellawell 1999	Moderate and severe; acute, 15–78 yo (39.2)	96	GOS (6 months)	GCS; PTA	Lower GCS; length of PTA	Univariate	None
Gomez 2000	Severe; acute, 15–>65 yo	810	GOS (6 months)	Age	Older age	Multivariate	None
Rovlias 2004	Severe; acute (isolated BI), 16- 70yo (40)	345	GOS (6 months)	GCS; age	GCS; age	Multivariate	None
Formisano 2004	Severe; rehab (coma >15 days), 11- 56 yo (26)	43	GOS (>1 year)	Length of coma; age	Length of coma; age	Univariate	None

**TABLE 14-3**  
*Elderly*

STUDY	POPULATION/ AGE	NUMBER	OUTCOME	PREDICTOR	FINDINGS ASSOCIATED WITH WORSE OUTCOME	STATISTICS	POTENTIAL "THRESHOLD" VALUES
Ross 1992	Acute; all GCS; age >65 yo	195	GOS (6 months)	GCS	Lower GCS	Univariate	Only 3 percent of patients with an initial GCS <8 achieved a good recovery. (CI 1–9 percent)
Kilaru 1996	Acute; severe; >65 yo	40	GOS (38 months)	GCS	Lower GCS	Multivariate	No patient with admission GCS <8 achieved a good recovery. (CI 0–8 percent)



**TABLE 14-4**  
*Penetrating Missile Injury*

STUDY	POPULATION	NUMBER	OUTCOME	PREDICTOR	FINDINGS ASSOCIATED WITH WORSE OUTCOME	STATISTICS	POTENTIAL "THRESHOLD" VALUES
Grahm 1990	Acute; all GCS	100	GOS (>6 months)	GCS; CT	Lower GCS; bilateral or trans-ventricular injury on CT	Univariate	No patients with GCS < 8 or transventricular injury had good recovery (CI 0–4 percent)
Levy 1994	Acute ; GCS 3–5	190	GOS (6–12 months)	GCS; CT	Lower GCS; bilateral injury with IVH on CT	Multivariate	No patients with GCS 3–5 had a good recovery (CI 0–2 percent)

**GCS:**

- Lower scores associated with worse outcomes
- No threshold values

**Length of Coma:**

- Longer duration associated with worse outcomes
- Threshold values:
  - Severe disability unlikely when less than two weeks
  - Good recovery unlikely when greater than four weeks

**PTA:**

- Longer duration associated with worse outcomes
- Threshold values:
  - Severe disability unlikely when less than two months
  - Good recovery unlikely when greater than three months

**AGE:**

- Older age associated with worse outcomes
- Threshold values:
  - Good recovery unlikely when greater than 65 years

**NEUROIMAGING:**

- Certain features (e.g., depth of lesions) associated with worse outcomes
- Threshold values:
  - Good recovery unlikely when bilateral brainstem lesions present on early MRI

a lower brainstem lesion made a good recovery), the confidence interval was too large to be included. There were, however, some differences in the findings of the two studies. The study by Wedekind (32) found that lesions in the basal ganglia and corpus callosum, as well as the total lesion burden in the brain, were associated with a worse outcome; the later study (34) did not find these associations.

*Discussion* The advantage of conventional MRI (relative to CT scanning) is that it allows for better visualization of lesions, especially those in the brainstem. As a result, MRI is ideally suited to study the centripetal model of brain injury severity (62) which claims that the stronger the forces to which the brain is subjected, the more severe the injury and the deeper the lesions. The findings of these two studies (as well as others that did not meet the inclusion criteria) are consistent with this hypothesis: depth of lesion is associated with worse outcomes because it is a marker of brain injury severity.

*Conclusions* If an MRI from the first several weeks after a TBI is available, the depth of the lesions (and, possibly, the total lesion burden) are associated with worse outcome. In particular, the presence of bilateral brainstem lesions makes the possibility of a good recovery very unlikely.

**CT**

*Summary* Ten studies (27–31, 33, 35–38) met the inclusion criteria; all but one were conducted in the acute care setting. However, even the study from the rehabilitation setting made use of the acute care CT scan. Almost half of the studies used scales that included several different imaging variables, making it difficult to isolate how individual variables contributed to outcome (two of the

**FIGURE 14-6**

*Summary of Studies of Nonpenetrating TBI*

threshold for the possibility of a good recovery: no one in their study with bilateral brainstem lesions made a good recovery (95 percent CI: 0–8 percent). Although the second study (32) reported a similar finding (i.e., no one with

studies used the Traumatic Coma Data Bank (TCDB) classification, one the intracranial severity score of the Abbreviated Injury Scale (AIS), and one a scale especially designed for the study). Nonetheless, certain patterns emerged.

Every study that looked at the presence of subarachnoid hemorrhage (SAH) as a variable found that it was associated with worse outcome. In addition, all but one of the studies that examined the presence of cisternal effacement or midline shift found they correlated with worse outcome. Finally, although the presence of epidural or subdural hematomas was correlated with worse outcome in the studies that included them as predictor variables, no more specific conclusions could be drawn, given the variation in how they were graded.

The two studies that used the TCDB classification reported threshold effects, although they differed in what they found. One study (31) found that no patient whose scan was classified as a “level VI” category (the worst rating) achieved a good recovery or moderate disability. The other study (36) found that no one with a “level I” scan (the best rating) did worse than moderate disability. However, the confidence intervals around both values were unacceptably large. In addition, neither study confirmed the finding of the other, rendering the reported thresholds unsupported across studies.

*Discussion* Since the acute care CT scan (or a report) is often available to rehabilitation professionals, it would have been helpful if the CT findings yielded more definitive prognoses. Unfortunately, although it is known that certain lesions are associated with worse outcomes, the nature of the relationship is such that more specific prognoses cannot be made. It may be that the use of more quantitative measures of CT lesions would yield better prognostic information, but this has not yet been demonstrated. Overall, all of these findings are consistent with those of the excluded studies.

*Conclusions* The presence of SAH, cisternal effacement, significant midline shift, EDH, or SDH on an acute care CT scan are all associated with worse outcomes. More specific conclusions about the implications of the lesions cannot be drawn, because each one individually can be associated with the full range of outcomes after TBI.

### Initial GCS

*Summary* Of the studies that met the inclusion criteria, ten (38, 41, 42, 45, 46, 48, 50, 53, 56, 57) examined the relationship between GCS and outcome. As mentioned earlier, studies that used only a subset of the GCS (e.g., motor score) were excluded because, although rehabilitation professionals should have access to the initial GCS score, the individual subscores would be much less available. All but

one of the studies found an association between lower GCS scores and worse outcomes. Although the studies measured the GCS differently (e.g., admission, post-resuscitation, highest in the first 6–24 hr, etc.), none of them discovered threshold or cut-off values for outcomes. In other words, any particular initial GCS score could potentially be associated with any outcome (although the chances of having a good outcome diminish as the GCS score is lower).

*Discussion* Although providing a general idea of the severity of the injury, the GCS by itself does not yield definitive prognoses. This is true even when the accuracy of the GCS is increased by varying the timing and content of measurement. Even the most accurate of the methods did not improve accuracy enough to allow for more specific prognoses. Also, rehabilitation professionals are often limited in which GCS score they have access to (and often don't know exactly when it was obtained). For both these reasons, it did not seem worthwhile to look more closely at the accuracy of different ways of obtaining the GCS. All of these findings are consistent with the rest of the literature (that is, the studies that were excluded).

*Conclusions* Although the initial GCS score is associated with outcome and lower GCS scores are associated with worse outcomes, one cannot draw more specific conclusions solely from the GCS score.

### Length of Coma

*Summary* Of the studies that met the inclusion criteria, there were six (27,39,41,44,53,55) that studied the relationship between the length of coma and outcome. Four of the six defined the length of coma as that period of time until the patient started following commands. The other two studies did not specify how coma duration was measured. All but one found a relationship between the duration of coma and outcome (the longer the duration of coma, the worse the outcome). In addition, one of the studies (53) reported its data in such a way that it was possible to determine a threshold value for excluding the possibility of a good recovery. Specifically, they found that no subject made a good recovery whose length of coma exceeded fourteen days (53).

*Discussion* Although the duration of coma has been defined several different ways (e.g., when GCS is 9 or above, when the eyes open, etc.), all the studies that reported their method of measurement used the time to follow commands. This was also the predominant method of measurement in the rest of the literature. Therefore, the rehabilitation clinician using the length of coma for prognostic purposes should follow the same guidelines. Only one study (53) reported a threshold value with an acceptable confidence interval. However, the

value of 14 days they found seems too short. For instance, the Tate study (44) reported instances of a good recovery even after a month of coma. Other studies, excluded in the review, also converge on approximately one month as a cut-off point (beyond which the chances of a good recovery are small) (63–65). In these studies, it appears that, on average, only 7–8 percent of patients will make a good recovery who are not following commands beyond one month.

*Conclusions* The longer the duration of coma (as measured by the time to follow commands), the more likely a worse outcome. In particular, a duration of coma greater than four weeks makes a good recovery unlikely.

### PTA

*Summary* Of the studies that met the methodological criteria, seven (27,44,50,51,53,55,57) investigated the relationship between the length of post-traumatic amnesia (PTA) and outcome. All but one found the two were associated (the longer the duration of PTA, the worse the outcome). Only two of the studies reported how they measured PTA (53,55); both of these studies relied on the Galveston Orientation and Amnesia Test (GOAT) to mark the end of PTA (i.e., a score of greater than 75 on two consecutive days). Two of the studies (50,53) reported their data in such a way that it was possible to determine threshold values for excluding the possibility of either a good recovery or a severe disability. Specifically, one of the studies found that no subject had an outcome of severe disability until their duration of PTA exceeded two months (CI 0–3.6 percent) (50). Similarly, the Katz study (53) found that only 2 percent of individuals with a duration of PTA less than two months was severely disabled (CI 0.3–8.8 percent). Although both studies converged on the period during which a severe disability was unlikely, they varied in when they were able to exclude the possibility of a good recovery. The longest reported duration of PTA before one could exclude a good recovery was three months (CI 0–11 percent) (53).

*Discussion* The duration of PTA has long been considered one of the most powerful prognostic factors available to the rehabilitation clinician (66). Besides its power, the duration of PTA has other advantages that make it especially useful. For one, the duration of PTA lends itself to the identification of threshold values. Also, many of these thresholds are crossed while the patient is in inpatient rehabilitation, allowing the rehabilitation professional an opportunity to substantively address issues of prognosis during the rehabilitation stay. In addition, because these thresholds are often reached in rehabilitation, the rehabilitation professional has much more control over the measurement of this variable.

In general, the studies that reported thresholds converge on a duration of PTA of 2–3 months when the prognosis becomes much clearer. For instance, both the Bishara (50) and Katz (53) studies agreed that the possibility of severe disability was very unlikely when the duration of PTA was less than 2 months. Also, both the Bishara (50) study (whose confidence interval was too wide to include) and the Katz (53) studies converged on 2–3 months as the duration of PTA before the possibility of a good recovery becomes very unlikely. A review of the studies on PTA that did not meet the inclusion criteria revealed findings consistent with this value.

*Conclusions* The longer the duration of PTA, the worse the outcome. In particular, it is unlikely that a person will have an outcome of severe disability if the duration of PTA is less than two months. Conversely, it is unlikely a person will have a good recovery when the duration of PTA extends beyond three months.

### Age

*Summary* Of the studies that met the inclusion criteria, seventeen (27,29,30,33,38,39,40,42,43,45,47,49,50,52–55) investigated the relationship between age and outcome. All but two (39,50) found the two were associated (the older the patient, the worse the outcome). There were differences in whether increasing age was seen as a continuous risk factor or whether the risk increased at certain ages (“inflection points”). Four of the studies (33,49,52,53) reported threshold values of an age above which a good recovery was extremely unlikely. However, there was variability in the exact age found to represent this cut-off point. Among patients with a severe TBI, two studies found that no patients had a good recovery after the ages of 55 (CI 0–4.1 percent) (49) and 60 (CI 0–6.9 percent) (52). Another study found that, although there were some patients with a good recovery after the age of 65, the probability was low (6 percent) (CI 2–14 percent) (33).

*Discussion* Age is a powerful prognostic factor. Although the risk for adults appears continuous, the prognosis worsens significantly after the age of 65. This is discussed in more detail in the next section. A review of the excluded literature is consistent with these findings.

*Conclusions* Older patients have a worse outcome after a severe TBI. In particular, in patients over 65, the chances of a good recovery after severe TBI are unlikely.

### Special Populations: Elderly

*Summary* There were two studies (58,59) meeting the inclusion criteria that examined prognostic factors in patients over the age of 65. Both studies found the initial

GCS was associated with outcome: the lower one's GCS score, the worse the outcome. One study (59) found that no subject with an admission GCS <8 had a good recovery at long-term follow-up (CI 0–8.2 percent). This is consistent with the studies mentioned previously (49,52) that also found no subjects over 65 who had a good recovery after a severe TBI.

The other study on the elderly (58), however, found that a subset of those with an admission GCS less than eight did have the potential to achieve a good recovery. Specifically, they reported that those patients who regained consciousness within 72 hours had the potential to achieve a good recovery (3 percent in their series) (CI 0.6–8.9 percent). This finding is consistent with the results of the other study mentioned previously (33) that found some patients over 65 who achieved a good recovery (6 percent in their series, with CI 2–14 percent).

*Discussion* The importance of TBI in the elderly is growing. This is not only because the incidence of TBI rises in the elderly but also because the percentage of the population over the age of 65 is growing. Although there may be confounding factors (e.g., co-morbidities), it is now clear that age is an independent risk factor in this population (67). There are many potential reasons for this, ranging from the nature of the injuries in the elderly (e.g., subdural hematomas) to changes in the brain as one ages (e.g., decreased functional reserve, less elasticity of blood vessels, etc.). These issues are discussed in more depth in the chapter on TBI in the elderly (Chapter 21).

For our purposes, the main point is that a good recovery after a severe TBI in a person over 65 is very unlikely. The increased likelihood of poor outcomes is also found in the other severity categories. In fact, several writers have noted that, in terms of outcome, a moderate TBI in the elderly resembles a severe TBI in a younger person (58, 68, 69). Even the outcomes of mild TBI in the elderly are much worse, with many never returning to their premorbid functional status (70).

*Conclusions* In patients over the age of 65, the lower the admission GCS, the worse the outcome. In particular, older patients who have sustained a severe TBI (GCS less than eight) are unlikely to achieve a good recovery.

### Special Populations: Penetrating Injuries

*Summary* There were two studies (60, 61) that met the inclusion criteria which investigated prognostic factors in civilian patients with penetrating missile wounds. Both studies found the GCS was associated with outcome: the lower one's GCS score, the worse the outcome. Both studies also found that CT findings of bilateral injury or trans-ventricular injury were associated with worse outcomes. One study (60) found that no patients who had a

post-resuscitation GCS score <8 had a good recovery at long-term follow-up (CI 0–4.4 percent). The other study (61) only included patients with GCS scores of 3–5. No one in their series achieved a good recovery at long-term follow-up (CI 0–1.6 percent).

*Discussion* Penetrating injury differs from closed brain injuries in many ways, as discussed elsewhere in this textbook (Chapter 18). In terms of outcome, the early mortality rate after penetrating injury is much higher than that of closed head injury (71). Among the survivors, however, there are proportionally fewer people who are left vegetative or severely disabled (71). Although many prognostic factors have been studied in penetrating injuries (71), only the GCS is readily available to rehabilitation clinicians. Unlike closed head injury, where a range of outcomes is still possible with a GCS of 3–8, in penetrating injury it is very unlikely that patients with an initial GCS in this range will have a good recovery. These findings are consistent with those in the excluded studies; only one study reported any patients who achieved a good outcome with an initial GCS of 6–8 (8 percent) (72). However, they also found no one achieved a good recovery with an initial GCS of 3–5.

*Conclusions* In patients with a penetrating missile injury, lower GCS scores and CT findings of bilaterality or trans-ventricular injury are associated with worse outcomes. Moreover, those patients with a post-resuscitation GCS score of 8 or less are unlikely to achieve a good recovery.

### Special Populations: Moderate TBI

The focus of this chapter is on severe TBI because it is with this group of patients that the most uncertainty exists about long-term prognosis. In contrast, outcomes after moderate TBI are much clearer (10,19): more than 90 percent of individuals with moderate TBI will achieve either a moderate disability or good recovery. This information is certainly useful for clinicians counseling family members, especially by reassuring them the odds are heavily in favor of at least independent living, if not a return to previous function.

There are certain risk factors associated with the poorer outcomes: lower GCS scores (e.g., 9 or 10), older age, and abnormalities on the CT scan (10,19). When these are present, patients are more likely to have a moderate disability (or, infrequently, even a severe disability) rather than a good recovery. This information can be used to adjust the content and tone of prognostic information provided to family members.

Although the prognosis after moderate TBI is good, it is here that the limits of the higher categories of the GOS are most obvious. Studies have shown that even individuals with a good recovery often have neurobehavioral

problems that contribute significantly to the morbidity of moderate TBI (10,19). It is important to communicate this information to the family, although initially it may be in the most general of terms (e.g., “most people are able to at least live on their own after this type of brain injury, although they may have some other problems”).

### Neuropsychological Testing

Although early neuropsychological testing (performed within one month after injury or at the resolution of PTA) was originally included as a potential predictor variable, none of the studies reviewed met the methodological criteria, mainly because of limited follow-up. Still, because neuropsychological testing is so widely used in the rehabilitation setting, the findings of some of these studies (64,73–77) are reviewed here. Almost all the studies found an association between selected test results and long-term outcome, even when adjusted for demographic and injury severity variables (64). The specific tests found to be predictive varied between the studies, however, limiting the utility of the findings. Another feature of the studies that reduced their applicability was the use of statistical analyses that cannot easily be utilized in the clinical setting (e.g., correlation coefficients, principal components analysis, etc.).

Even when the findings were reported in a clinically useful way, the studies were still not helpful. This is because early neuropsychological testing, even when correlated with outcome, is not a particularly powerful predictor. In the language of the rest of the chapter, there were no threshold values that were found for neuropsychological test scores. For instance, one study (75) found that a normal score on one of ten tests identified as predictive still had less than a 50 percent chance of predicting productivity at one year or beyond. Even an impaired score, which was a more powerful prognosticator, predicted lack of productivity in only 70 percent of people. The utility of testing is further diminished by the fact that only a subset of patients are able to be tested subacutely; therefore, the results of these studies are not relevant to the significant number of patients who are not testable during inpatient rehabilitation.

In fact, this distinction between those who are testable or not (rather than the test scores themselves) turns out to be the most powerful predictor in these studies and one that could potentially serve as a threshold value for prognosis. In one of the two studies that examined this relationship (75), only 6 percent of patients who were unable to complete any test during inpatient rehabilitation were productive at one year. In the other study (64), only 6 percent of those who were not testable at one month were employed a year later. In contrast, being testable was not as predictive in either study, correctly classifying only about 40 percent–80 percent of those who

would be productive at one year. Although the inability to be tested in the subacute setting appears to be a potentially valuable prognostic variable, it does not provide significantly more information than the better supported use of length of coma or duration of PTA.

Indeed, it is likely that the findings in these studies were confounded by the length of coma or PTA. For instance, the first study was designed so that people were only tested when they emerged from post-traumatic amnesia. Thus, being testable was a marker for the length of PTA. The primary reason that patients who are not testable during inpatient rehabilitation do poorly is that they have a prolonged PTA. Assuming that most patients are discharged from inpatient rehabilitation about 2–3 months after their injury, those patients who are not testable during this period must have had lengths of PTA greater than 2–3 months, which was the threshold value identified in the previous studies. Similar considerations apply to the other studies (63,64). There was one study that did adjust for PTA duration; it found that neuropsychological test performance made a contribution to the prediction of productivity beyond that made by the duration of PTA (76). The exact improvement in predictive power made by the tests was not reported, however, and is unlikely to be clinically significant.

In conclusion, it is likely there is an association between early neuropsychological test performance and long-term outcome. More specific conclusions cannot be made because of the methodological limitations of the studies, the lack of consensus on which tests are most important, and because, even with the most robust results, there are no threshold values for test performance. The only statement that can be made with some confidence (within the constraints of the methodological limitations already discussed) is that not being testable early on is a poor prognostic sign for a productive long-term outcome. This subject is more extensively reviewed elsewhere (77).

### Summary

The 35 studies were almost unanimous in finding that age, initial GCS score, length of coma, duration of PTA, and neuroimaging findings are correlated with outcome (Figure 14–6). However, this represents information that TBI clinicians already know. Of much greater interest is the existence of threshold values for several of the variables; these allow the clinician to formulate more fine-grained prognoses in individual cases. Specifically, age, length of coma, and duration of PTA all provide valuable information the clinician can use to mark milestones when either a severe disability or a good recovery are unlikely. These results are based on a small number of studies (less than a third of the total), however; this must be kept in mind when using this information in clinical situations. On the other hand, the fact that these results were consistent

with those in the excluded studies increases one's confidence in the findings. In essence, the results are at least consistent with almost *all* the published literature.

There was only one minor exception to the general agreement between the included and excluded studies: the maximum length of coma after which a good recovery is extremely unlikely. The original review found a value of two weeks. However, as mentioned above, there were several excluded studies that found a significant number of individuals with a good recovery after two weeks of coma. These other studies seem to converge on the value of one month of coma as the time after which a good recovery is very unlikely. Because of the wish to err on the side of preserving hope, one month of coma was adopted as the final threshold value for length of coma (Figure 14-7).

Finally, the statistical uncertainty involved must be kept in mind. The upper limits of the confidence intervals for the threshold values averaged approximately 7 percent. This means that, on average, up to 7 percent of individuals could have outcomes that are considered unlikely (e.g., up to 7 percent of patients with a PTA greater than 3 months may have a good recovery on the GOS). This underscores the point that one should use terms such as "unlikely" or "very unlikely" rather than, for instance, "never" in talking with families. One may even want to convey the associated degree of uncertainty in quantitative terms.

### Applying the Guidelines

The final guidelines are presented in Figure 14-7. They are based both on the results of the initial review as well as, for length of coma, the findings of the excluded studies. Also, only findings supported by more than one study were included; this meant the results of the MRI study were not part of the final guidelines. There are a few final points about applying these principles. The first is simply to recommend the use of the different sources of information at different times in the recovery process. For

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|--|
| <p>Severe disability (according to GOS) is unlikely when:</p> <ul style="list-style-type: none"> <li>• Time to follow commands is less than two weeks</li> <li>• Duration of PTA is less than two months</li> </ul> <p>Good recovery (according to the GOS) is unlikely when:</p> <ul style="list-style-type: none"> <li>• Time to follow commands is longer than one month</li> <li>• Duration of PTA is greater than three months</li> <li>• Age is greater than 65 years</li> </ul> |
|--|

\* See text for important qualifications

**FIGURE 14-7**

*Summary of Evidence-Based Guidelines for Prognostication After Severe TBI\**

example, if someone older than 65 years has a severe TBI, one knows fairly early that the chances of a good recovery are low, especially if they do not regain consciousness within a few days. For those under the age of 65, however, one will probably need to wait until the duration of coma is known (especially when it is less than two weeks or greater than 4 weeks). Later, because of its predictive power, the length of PTA should be used as the primary source of information.

This sequential use of different variables is important not only because the later variables are more powerful than the earlier ones. It is also necessary because there is not always a strong correlation between the variables (e.g., between the length of coma and duration of PTA). For instance, based on clinical experience, one can have a duration of coma of less than two weeks (which would imply a relatively good prognosis) with a protracted PTA of greater than 2–3 months (which implies a worse prognosis). In these cases, the prognosis based on the duration of PTA should be used as the primary source of information. It is also important to keep in mind some sense of the trajectory of recovery and adjust one's predictions accordingly. In someone who is still minimally conscious at two months, for instance, it is extremely unlikely they will become fully conscious and clear from PTA within the following month. Thus, one does not always have to wait until the passage of a full three months to infer that the likelihood of a good recovery is low.

Finally, it is also important to modify one's predictions based on the presence or absence of significant focal lesions. Although it is true that almost all the studies "correct" for the presence of focal lesions (by including both those with and without such lesions), knowledge of a significant focal lesion can help with prognostication in individual cases. Someone with a left anterior lesion and significant language deficits will likely have a worse outcome than patients who have similar lengths of coma, PTA, etc., but who don't have the same focal lesion. On the other hand, it has been shown that patients who primarily have diffuse axonal injury usually do worse than those whose primary lesions are focal (53). If the predominant underlying pathology is known, clinicians can use this information to modify what they tell patients and their families. In summary, application of the principles presented here involves the sequential use of the predictor variables, modified by knowledge of the larger trajectory of recovery as well as the presence or absence of significant focal lesions.

### COMMUNICATING PROGNoses

*Patients and their families will forgive you for wrong diagnoses, but will rarely forgive you for wrong prognoses.*

*David Seegal*

### Barriers to Communication

Formulating a prediction constitutes only part of the clinical act of prognosis; this information must then be communicated to patients and families. Clinicians' reluctance to communicate this information is just as responsible for the neglect of prognostication as is the difficulty in developing a prognosis in the first place. There are many reasons for this reluctance. Many health care professionals believe that patients and families don't want prognostic information (4). Yet, studies have shown that professionals significantly underestimate patients' and families' desire for this information (78–82). One study found that 88 percent of patients wanted prognostic information (83). Another study showed that, even when patients had not explicitly asked for prognostic information, they wished the clinician had discussed it with them (84).

Although none of these studies were specifically related to TBI (most were in oncology), there is no reason to believe the findings would be any different in brain injury. As mentioned earlier, families have identified information about the future as one of their greatest needs in the aftermath of a TBI (1–3). Of course, it is true some patients or their families sincerely do not want prognostic information (85). It may even be true that these preferences may vary by one's ethnic or cultural group (85). Therefore, one of the key steps in communicating prognoses is to find out how much information the patient or the family wants.

Another reason that rehabilitation professionals may be reluctant to discuss prognosis is the fear that families will interpret any discussion of uncertainty as evidence of the clinician's lack of competence (86). There is some support for this concern: one study found that the presentation of probabilities in discussing possible outcomes undermined patients' confidence in their physicians (87). In addition, there is evidence that clinicians themselves are unable to tolerate uncertainty (88); this is likely to contribute to their avoidance of prognosis.

Rehabilitation professionals may also believe that communicating a poor prognosis to patients or families causes too much pain, thereby extinguishing hope that might be needed to actively engage in rehabilitation. Yet studies in other contexts at least partially belie this concern. One study found that, although communicating a poor prognosis did result in short-term distress among cancer patients, they experienced less anxiety, more peace of mind, and better adjustment in the long-term (80). It might even be the case that not being told about a poor prognosis interferes with the grieving process by making it much more ambiguous (since one is not sure whether a loss has occurred). There is evidence this "ambiguous grief" results in more emotional distress than grief where the loss is both clear and acknowledged (89).

Finally, avoiding a discussion of prognosis can itself cause distress: the anxiety associated with uncertainty often compounds the suffering families experience. Of

course, like everything else in medicine, the benefits of communication must be weighed against the risks; however, in most cases, it is probable that more is gained by open communication (4). This is not to say that minimizing distress and fostering hope are unimportant. Rather, it is to highlight the fact that the avoidance of prognosis is unlikely to achieve these goals. There are better means by which to foster hope; some of these ways will be discussed shortly.

Not only are clinicians concerned about the distress they might cause families, they themselves feel distress in communicating poor prognoses (4). Clinicians (especially physicians) might feel unprepared to deal with the emotions the patient or family might express. Also, it has been argued that conveying a poor prognosis reminds clinicians of the limits of their abilities (since they are powerless to change the outcome) and this also reduces their willingness to have these discussions. Finally, the fact remains that most clinicians (again, especially physicians) are simply not trained in "how to break bad news" (78). Their reluctance stems from not knowing *how* to proceed (compounded by their apprehension in publicly performing a skill they have not mastered).

It is hoped the guidelines presented here (summarized in Figures 14-8–14-10) will help allay some of this anxiety and improve the frequency and quality of communication of prognostic information. Several general guidelines for communicating prognostic information are presented in Figure 14-8; these guidelines will structure the discussion to follow.

### Guidelines for Communicating Prognoses

*Begin with the Patient and Family* Although most patients and families want prognostic information, this is not universally true. Even those who want to discuss prognosis may differ in the amount of information desired as well as how its delivery is timed. Thus, if patients or families don't explicitly ask to discuss prognosis, it is important to ask if they are interested in the information. If so, one should explore in more detail what they are interested

- Begin with the family's desire for information as well as their current beliefs.
- Ensure that the meaning and content of the outcomes are understood.
- Present quantitative information in a manner that can be understood (see Figure 14-9).
- Foster hope.
- Pay attention to the process of communication (see Figure 14-10).

**FIGURE 14-8**

*General Guidelines for Communicating Prognostic Information*

- Try to use “natural frequencies” when communicating probabilistic information (e.g., “Eight out of ten people with this type of injury will make a good recovery”)
- Present information both qualitatively as well as quantitatively (e.g., “This is a very good chance of a good recovery”)
- Attempt to “frame” information in both a positive and negative manner (e.g., “That is the same as saying that two out of ten people with this type of injury will not make a good recovery”)
- When possible, consider presenting the information visually.
- Ask person to restate, in their own words, their understanding of the information provided

FIGURE 14-9

*Guidelines for the Communication of Quantitative Information*

- Find a quiet, comfortable room without interruptions
- Sit close and speak face to face
- Have the family member's support network present, if wanted
- Present the information at a pace the family can follow
- Periodically summarize the discussion to that point
- Periodically ask family member to repeat or summarize what was said
- Keep the language simple but direct, without euphemism or jargon
- Allow time for questions

FIGURE 14-10

*Guidelines for the Communication Process*

in (for instance, in terms of possible outcomes). It is also helpful to begin by asking the family members what they already know and what their current perceptions are. This enables the clinician to build on the knowledge they already have or, if appropriate, correct any misinformation that might distort their understanding of the information to follow. Starting with the patient or family's desires and beliefs not only ensures that the discussion addresses their needs, but it also draws them into the conversation early (and thus hopefully makes it easier for them to articulate their concerns). It also gives them some sense of control in a situation where they often feel powerless.

**Ensure Understanding of the Outcomes** It is important that families clearly understand the nature of the outcomes discussed. This is especially important when one is using studies that rely on the GOS. The names of the GOS

categories can be confusing. In particular, the terms moderate and severe disability may imply a far worse prognosis than might actually be the case. Most families would not necessarily consider someone who can live independently and use public transportation moderately disabled, even if they can't work. Or, a person who might be independent in mobility and self-care might not be considered severely disabled, even if they were unable to live independently for cognitive reasons. Given this ambiguity, it is best to avoid the GOS category names altogether, and simply describe concretely what the outcomes might be. It is also important to mention some of the limitations of the GOS. Families should be aware that patients who achieve a good recovery might still have significant emotional or behavioral issues. At the same time, they should also know that the category of severe disability does not automatically preclude a good quality of life. One study found that almost half of individuals classified as severely disabled by the GOS at one year were satisfied with their lives (and close to a third who had made a good recovery were dissatisfied with their lives) (90). Finally, it is important to stress to families that most of the studies on prognosis followed patients for only a year, on average, and that there is evidence for continued gains well beyond that time (15).

**Present Statistical Information in an Understandable Manner** Prognostication is not only about the range of possible outcomes but also the likelihood of their occurring. Therefore, the ability to convey the numerical aspects of the information accurately is crucial. However, there are significant barriers to effective communication of quantitative information. The level of numerical literacy (“numeracy”) in the general population is low (91). Even the understanding of the most elementary ideas of probability cannot be taken for granted. In one study, only half the respondents were able to predict the results of tossing a fair coin 1000 times. The same study found that only 16 percent of respondents correctly answered all three of a set of basic numerical questions (92). These findings have been reproduced in other studies (93).

People had the most difficulty with concepts such as relative risk (94), odds, rates (where the numerator is fixed at 1 and the denominator varies) (95), and proportions where the denominator was anything other than 10 or a 100. One common problem is that people often pay attention only to the numbers and not the form they are in. That is, they believe that the expression with the highest number must represent the highest probability, regardless of whether it is expressed as a rate, proportion, percentage, etc. In one study, subjects rated a health problem as riskier when told that it affects 1,286 out of 10,000 people compared to one that affects 24.14 out of 100 people (96). Other times it is not clear why people are having difficulty. For instance, in another study, half the



respondents believed that 2.6/1000 was a larger number than 8.9/1000 (94). Converting between proportions and percentages was particularly difficult (92,97). In summary, there is a significant chance for confusion when the likelihood of outcomes is communicated by concepts such as rates, proportions, etc.

However, the most common way of communicating prognostic information, both in studies and in clinical practice, is through the uses of percentages (e.g., “there is a 70 percent chance he will be able to go back to work”). Yet the comprehension of even such a seemingly straightforward concept as percentages cannot be taken for granted. One study that assessed the understanding of the phrase “there is a 30 percent chance it will rain tomorrow” found that two thirds of the subjects misinterpreted the statement (for instance, believing it meant that it will rain just 30 percent of the day or in 30 percent of the area) (98). The problem here has less to do with numbers and more with an understanding of the referent class—what the percentage is about (e.g., believing that it refers to a portion of the day or the geographic area instead of the likelihood of any rainfall). Even when it seems clear to professionals what the referent class should be, patients can be confused. In one study where patients were told “your risk of developing breast cancer is 10 percent”, one subject asked “10 percent of what?” (99). Besides confusion about the referent class, there are other logical or conceptual difficulties that people can have with percentages. For example, a study found that some people thought the risk of developing and dying of breast cancer was higher than the risk of simply developing breast cancer (100).

In addition to the conceptual issues, problems even arise with the numerical aspects of percentages. In looking at cumulative risks (which required addition), many subjects in one study ended up with totals greater than 100 percent (100). In another study of people who were “highly educated”, 20 percent of the respondents were not able to state which represented the larger risk: 1 percent, 5 percent, or 10 percent (93). Thus, when communication about prognoses involves the use of percentages, it cannot be automatically assumed that patients or families understand this information.

The difficulty in understanding numerical information is further compounded by the quantified uncertainty associated with any prediction. That is, not only is the primary outcome itself expressed as a probability (e.g., “your son has a 70 percent chance of living independently . . .”), but this estimate itself is subject to uncertainty (“ . . . and we know this with 90 percent certainty”). Having to process two different levels of numerical uncertainty can overwhelm families and patients and, thus, ironically, end up disempowering decision-making rather than enabling it (87). These expressions of uncertainty can also undermine confidence in the clinician (87), as discussed earlier.

In the end, the numbers themselves may not even be used in decision making. Several studies have found that people immediately code numbers they hear into qualitative or ordinal categories such as high, medium, or low probability or even simply “likely” or “not likely” (86,94,96). Moreover, there is evidence the categories people use were better predictors of their decision making than the actual numbers they were given (94,96). Others have found the form of the information (numerical vs. qualitative) did not affect decision making (101). These findings raise the issue of whether professionals should be communicating numeric values to patients and their families in the first place, rather than using qualitative statements such as likely, unlikely, probable, etc.

In fact, studies have shown that about a third of people would prefer that information about the likelihood of future events be given in qualitative terms rather than numerically (102,103). The problem with qualitative information, however, is that there is a wide variation in the interpretation of the terms, both among patients as well as professionals. One study found that the range of values patients associated with the word “frequent” was 30 percent to 90 percent (102). A report on the understanding of these terms by professionals finds that, for example, the range of values associated with the term “unlikely” was .05 to 90 percent (104). A study that compared the understanding of clinicians and patients found that they differed by an order of magnitude in the numerical associations they made to the same qualitative terms (105). These findings suggest that any use of descriptive terms would need to be supplemented by numeric information, even for those patients who prefer that information be presented qualitatively.

In addition to numeric and qualitative *verbal* communication, there is evidence that graphic displays may also aid in communicating numeric information (106). However, very few studies have directly examined which format might be the most effective. One study that did investigate this question found that a row of ten human stick figures (shaded and unshaded to represent the percentages involved) was the most easily understood graphic and preferred by most of the subjects (99). This is an area needing further study.

So far the discussion has focused on how the quantitative content of information is presented, whether descriptively, numerically, graphically, etc. Yet, non-quantitative aspects of the message can also affect a person’s perception of how likely an event is to occur. For example, one could state that a patient has a 10 percent chance of having a good outcome or a 90 percent chance of having a poor outcome. Almost universally, people perceived a good outcome as being more likely when presented with the “positive” statement (“10 percent chance of good outcome”) than when presented with the “negative” statement, despite both being numerically equivalent. These

findings are the result of “framing” effects, the most widely studied of which has been the “positive/negative” or “loss/gain” frame, as in the example above. A recent review found that, while framing effects did exist, their effect on patients’ understanding was much less than that of the “innumeracy” described earlier (107). Still, the existence of framing effects has implications for how prognostic information might be communicated in TBI, as will be seen below.

Although the discussion so far has primarily been about patients and families, it should be pointed out that professionals, especially physicians, often have the same problems in handling quantitative information. Studies have found that physicians are subject to positive or negative framing effects in their treatment decisions: when the same numeric data were presented in a positive frame, physicians were more likely to undertake the treatment (108). Other studies have demonstrated that the way in which the results of clinical trials are reported will affect physician prescribing practices, even when the results themselves are identical (108). For instance, physicians are more likely to prescribe medications if efficacy is presented as a relative risk reduction instead of an absolute risk reduction (109,110). With regards to the qualitative use of probability terms, there is just as much variability in physicians’ understanding of these terms as is found with laypeople (104). Finally, there is widespread acknowledgement of the difficulties most physicians have in understanding other statistical concepts, including concepts used routinely in journal articles and even clinical practice (111,112).

*Practical Suggestions for Presenting Statistical Information* Given the significant barriers to the communication and comprehension of numeric information, what is the best way for a professional to proceed? One solution would be to minimize the occasions in which this information would need to be presented. Clinicians could avoid these discussions during those periods of the recovery process when there are a wide range of possible outcomes. Because each of these outcomes will be associated with a different likelihood of occurring, a discussion would involve the presentation of many different probabilities, further compounding the difficulties patients and families have with quantitative information. One of the advantages of threshold values is that they minimize the cognitive demands on comprehension. To tell a family that it is extremely unlikely the patient will be severely disabled or, alternatively, that it is now extremely unlikely they will have a good recovery, is comprehensible and requires minimal numeric abilities to understand. During periods before these milestones are reached, clinicians could avoid discussing the probabilities of particular outcomes and rely on more general statements such as “All we can say at this point is that there is a chance that she

will be able to return to work; we will know more later, as further information becomes available”.

Some families, however, will request detailed information even before milestones are reached. Or, even after a threshold has been crossed, they are interested in the likelihood of a moderate disability on the one hand and either a severe disability or good recovery, on the other. In these cases, there are some general principles that a TBI professional can follow to maximize the chances of comprehension (Figure 14-9). The first suggestion addresses the issue of what form the numeric information should be communicated in. As mentioned earlier, most people have significant difficulties with odds, rates, risks (especially relative risks), etc. Even percentages can be confusing for many people (100). The form of communicating numeric information that seems least susceptible to misunderstanding is the use of natural frequencies (98,99,112). In essence, a natural frequency describes the number of people out of an easily comprehensible set (e.g., 10 or 100) that have the outcome of interest. For instance, rather than state “There is an 80 percent chance your son will have a good recovery in a year”, one would say “Out of 10 people like your son, eight of them will have a good recovery in a year” (98,99,112).

As professionals, we are so used to converting one expression into another that we may no longer perceive the differences between these two formulations. There are, however, two important differences between using natural frequencies and using percentages. First, from a numeric point of view, people have more difficulty with percentages than they do with proportions (as long as the denominator is either 10 or 100 and is kept constant). This is not the only issue, however. To see why, compare the two expressions: “Your son has an 8 out of 10 chance of having a good recovery” and “Out of 10 people like your son, eight of them will have a good recovery”. Even though both formulations use proportions, people have much less difficulty with the second formulation.

This is because the second formulation specifies the referent class. By making it explicit that one is talking about people, the ambiguity that might result in questions such as “80 percent of what?” can be avoided. It also relevant that the referent class refers to persons instead of outcome categories. There is increasing evidence from cognitive psychology that people are better able to handle computations if they involve persons rather than abstract concepts (98,112). This was also seen when physicians were asked to solve questions of probability involving diagnostic testing (112).

Another suggestion to improve the communication of quantitative information would be to present the information through different routes; not just numerically, as just discussed, but also qualitatively and visually. Because most studies show that people are equally divided in how they wish to receive information, it would make sense to

rely on more than one modality. And the fact that people might have difficulty even in their preferred modality justifies presenting the information in at least two different ways. So, in the example cited, after the information was presented numerically, one might say “This is a very good chance for a good recovery”.

In addition, given the known effects of framing on the perception of information, one can consider framing the information both positively and negatively. One might say “This means that 2 out of 10 people in his situation will not have a good recovery”. Although framing information both positively and negatively might ensure better understanding of the actual likelihood, it could be argued that clinicians should rely mainly on positive framing so as to maximize hope (see below). Finally, as with any other medical interaction, it is helpful to ask the patient or family members to state, in their own words, their understanding of the information.

*Fostering Hope* The recommendation to foster hope may seem out of place in a discussion of *techniques* for communicating prognostic information. However, hope is an important part of this process. Of course, hope is most relevant when there is uncertainty. When the eventual outcome is fairly clear (e.g., PTA duration of several days), hope is less relevant precisely because of the certainty of the outcome. In contrast, when the outcome is uncertain (and an undesired outcome is possible), hope becomes correspondingly more important. Fostering hope has many advantages. For one, it may help patients and families to mobilize their energies and resources to engage fully in rehabilitation. In addition, when the prognosis is likely to be poor, even a little hope may “cushion the landing” and allow family members more time to process and come to terms with the probability of a poor outcome. Finally, based on clinical experience, most families seem far more upset with clinicians who offered them little or no hope when the outcome turned out well than those who offered some hope when the outcome was poor.

Of course, there are risks to offering hope, most notably the fear it might prevent family members from adequately preparing for a poorer outcome than they expect. However, the standard advice to families to “hope for the best but plan for the worst” (113) should allow most families to prepare for an undesired outcome without losing hope. When the concern about lack of adequate preparation persists, the clinician can always engage the family in another conversation, trying to shift their perspective. Overall, it appears that the benefits of offering hope in prognosis outweigh the risks (at least in most situations).

It was the commitment to fostering hope that was partly responsible for the emphasis on threshold values in this chapter. For instance, the interest in the longest period of PTA before one can reasonably exclude the possibility of a good recovery was motivated by the wish to

preserve justified hope as long as possible. Likewise, being able to tell family members that the chances of severe disability were unlikely if a patient emerged from PTA within a particular time frame helps to allay fears about the possibility of an especially “bad” outcome. The disadvantage of threshold values is that one has to wait until the milestones are reached before one can provide families with more precise information. One way to minimize the frustration of families during the period before a threshold value is crossed is to describe concretely what the potential outcomes are. This is much more helpful and reassuring than saying “we’ll just have to wait and see what happens”. Knowing what the outcomes might be gives families some sense of control (if only cognitive), while preserving hope for a favorable outcome.

Another way in which to convey hope involves framing the information in a positive way by presenting the likelihood of the favorable outcome rather than the unfavorable outcome (e.g., by saying “he has an 80 percent chance of a good outcome” instead of “he has a 20 percent chance of a poor outcome”). One could also accentuate the positive aspects of less favorable outcomes. For instance, one could point out that someone with a severe disability may still be independent in mobility and self-care. Or that there is not a strong correlation between disability category and quality of life. Or that people with traumatic brain injury are usually fairly healthy. In addition, emphasizing that improvement continues beyond the first year (the end point for many of the studies discussed) is another way of providing encouragement. Even the uncertainty in the prognosis can help to foster hope; by carefully highlighting this uncertainty, one can salvage a little hope even when the prognosis is particularly poor. One could even provide a rough numerical estimation of this uncertainty, based on the confidence intervals discussed earlier (e.g., “Although it is possible that up to 5 percent of people in his condition could have a good recovery, it is extremely unlikely”). Finally, it is important to reassure the family they will not be abandoned and that the clinician will be available to them during the long period of recovery (if true).

*Optimizing the Process* There have been several good reviews on improving the process by which this information is communicated, especially in the case of “bad news” (78–80). Some of these guidelines are summarized in Figure 14-10 and are self-explanatory.

## RECENT DEVELOPMENTS

*Predictions are difficult, especially about the future.*  
Yogi Berra

This chapter has focused on “classical” predictors of outcome after TBI. This was motivated by the wish to focus

on variables that are easily accessible to rehabilitation professionals. In addition, there is a much larger body of literature available for these variables than for more recently discovered prognostic factors. Still, rehabilitationists should be aware of these recent developments as they are likely to affect clinical practice over the next several years. Several of the most promising of these prognostic variables are discussed below: magnetic resonance spectroscopy (MRS), serum 100b assays (s100b), and apolipoprotein E (APO E) status. The one other modality that might have been included here is the use of evoked potentials in prognostication; however, this topic is covered elsewhere in this book (see Chapter 13).]

### MRS

Magnetic Resonance Spectroscopy (MRS) is a noninvasive modality that provides information about the neurochemical status of the brain. As such, it provides physiological information that appears to correlate more strongly with neuronal dysfunction than the structural information provided by conventional MRI. MRS allows one to measure the quantity of compounds thought to be markers of neuronal damage, whether from inflammation, impaired energy metabolism, neuronal death, myelin breakdown, etc. Examples include N-acetyl-aspartate (NAA), choline (Cho), and creatinine (Cr). Changes in the quantities of these compounds (or the ratio between them) correlate with the extent of cellular damage after neural insult.

Although this modality has been studied in many neurological disorders, its use in TBI is just beginning (114). Studies have already shown, however, that people with TBI and controls differ in the amount of these various compounds and that the relative concentrations correlate with *concurrent* neuropsychological performance (115) or GOS category (116). Other studies have demonstrated that certain variables (e.g., decreased NAA/Cr, decreased NAA/Cho, and increased Cho/Cr) correlate with other markers of injury severity (such as GCS and PTA) (117). Even more importantly, studies have shown that concentrations of these compounds seem to correlate with later outcomes, such as GOS at 6 months.

Several studies have found that MRS studies performed in the subacute period (approximately 6 weeks post-injury) correlated with outcome at 6 months or longer. For instance, either total gray matter NAA (118,119) or white matter NAA/Cr (120) correlated with both neuropsychological outcome (118,119) as well as outcome on the GOS (118,120), at 6 months. Other studies found that MRS scans done in the acute period also correlated with long-term outcome. One study found the NAA/Cr ratio acquired about two weeks after injury correlated with outcome on both the GOS and DRS at six months (121).

Besides the general finding that MRS variables correlate with later outcomes, several studies found

threshold values that seem to discriminate between various possible outcomes. One study reported values of gray matter NAA above which no one had less than a good recovery and below which no one had a good recovery (118). Another study found minimal overlap in the white matter NAA/Cr values between those subjects with severe disability, moderate disability, and good recovery (121). Finally, several studies investigated the improvement in accuracy gained by using MRS data instead of traditional clinical variables. For instance, one study in children found the presence of early (one week) lactate correctly classified children into either a good recovery/moderate disability or a poor recovery 96 percent of the time (versus about 80 percent accuracy with traditional clinical variables) (122). Another investigation also found that early (one week) MRS variables improved accuracy over clinical variables from 72 percent to 84 percent (123).

Although the results of these studies are promising, several caveats must be kept in mind. First, all of these studies were exploratory and met few of the methodological criteria used in this chapter. In addition, although several of the studies demonstrated that acute MRS variables were more accurate than other acute variables (such as GCS, pupillary abnormalities, etc.), no study has compared the accuracy of MRS variables to the even more powerful clinical variables that are available later (e.g., duration of PTA). Despite these current limitations, MRS is potentially a powerful aid to clinical prognostication after TBI.

### Serum 100b

Many serum markers have been proposed as prognostic factors after traumatic brain injury. These include serum 100b protein, neuron-specific enolase, interleukin 6, cleaved tau protein, and glial fibrillary acidic protein. Of these, the most promising work has involved serum 100b protein (S100b), which is found predominantly in astroglial cells. After a brain injury, increased levels of this compound are found in the blood as damaged glial cells release serum 100b across a disrupted blood-brain barrier. The protein is released immediately and peaks early; as a result, most investigators believe that only very early values (within hours after a TBI) are helpful in prognostication. As with MRS, serum 100b has also been studied in other neurological disorders such as anoxic brain injury.

Studies in traumatic brain injury have shown that early S100b levels correlate with the severity of injury (124,125) as well as the extent of abnormality seen on neuroimaging (125–129). More importantly, there are now many studies that suggest that early S100b values help predict long-term outcome as measured by the six month GOS category or neuropsychological test performance (127–133). Other studies have demonstrated that early S100b values are also correlated with outcome at

one year, both on the GOS (134–136) as well as on quality of life measures (134).

Most of these studies reported cut-off values for S100b levels that help distinguish between favorable (usually moderate disability/good recovery) and unfavorable outcomes (usually severe disability or death). They also reported the sensitivity, specificity, vegetative state, and positive and negative predictive values of the different cut-off values chosen. In general, the values chosen had high specificities (over 90 percent) and moderate sensitivities (around 70 percent). In other words, when S100b values are higher than the threshold levels chosen, there is a 90 percent chance of an unfavorable outcome. On the other hand, serum values below the cut off values are not as helpful because as many as 30 percent of patients with values below the threshold can still have an unfavorable outcome. Of course, the values chosen can be adjusted to increase either the sensitivity or specificity (but always at the expense of the other). Most of the studies being discussed compared the accuracy of predictions based on S100b levels with those based on other variables such as GCS, imaging abnormalities, etc. In almost every case, the S100b value was the most powerful predictor of outcome (137). Finally, although the discussion so far has focused on severe injuries, there is interest in using S100b values to predict which patients are at the highest risk of developing persistent post-concussional symptoms after a mild TBI (138–141).

Although all of these results are encouraging, they are still preliminary. As with the studies on MRS, almost none of the studies met the methodological criteria used in this review. In addition, the studies that reported the relative superiority of S100b compared the accuracy of S100b levels to values of *isolated* acute care variables rather than to a *combination* of these factors (which are known to be more powerful). Another significant concern about the use of S100b assays is the accumulating evidence that there are significant extracranial sources of S100b. These include soft tissue and bone, which are often damaged by the same incidents that result in TBI (142). As a result, there is a concern that previous studies may not have adequately controlled for these extracranial sources of S100b; this issue is still being debated. Finally, since the serum 100b level must be drawn within a short period after the injury, it is only of use to the rehabilitationists if they have access to results from the acute care setting. Despite these concerns, S100b values are potentially a powerful aid to prognostication after TBI.

### Apolipoprotein E

Apolipoprotein E plays a number of different roles in the human brain, many of which are not completely understood (143). Although its role in Alzheimer's disease has been known for a long time, there is now evidence this

lipoprotein can affect outcome after TBI. Early studies suggested that possession of the E4 allele was associated with a worse outcome after TBI. One study found this allele over-represented in patients who were still vegetative after one year and that presence of the E4 allele was a better predictor of outcome than the duration of coma (144). In another early study, patients with the E4 allele were more than twice as likely to have an unfavorable outcome on the GOS as those without the allele, even when adjusted for age, CT findings, and initial GCS (145). A different study found that, although the risk of severe disability was not associated with the presence of the E4 allele, the chances of having a good outcome were lower in the E4 group, even when controlling for age or duration of unconsciousness (146).

Despite these early findings, more recent studies have demonstrated either a smaller effect of the E4 allele or no discernible effect. Although a recent study reported a lower FIM motor score in carriers of the E4 allele, the difference was clinically small and was not found in the cognitive FIM score (147). Other studies found no association between the presence of the E4 allele and GOS outcome at 6 months (148,143). However, in the latter study (143), this may have been a result of the population studied (South African blacks); all the previous studies were done in caucasian populations and it is known that the impact of the E4 allele varies by race, at least in Alzheimer's disease.

Thus, the results of the studies done so far have been inconsistent. It seems fairly clear that the E4 allele does modify some end-points such as hematoma size (149), performance on a few neuropsychological tests (150, 151), or the development of late post-traumatic seizures (148). Its effect on more global outcome measures, however, is less pronounced. More importantly, the effect is not large enough to significantly improve clinical prognostication. Rather, the value of these findings will more likely be in identifying targets for intervention in the pathophysiology of TBI.

### Neural Networks

All the advances discussed above involved new types of information or data that were not previously available. But there is also some interest in different ways of analyzing already available information. All the studies discussed in this chapter used traditional statistical methodologies such as linear regression or decision trees. The use of newer statistical methodologies holds out the hope that more accurate predictions can be made than with conventional statistical methods. Probably the most promising of these new methods are neural networks. A neural network is a system of mathematical models that attempt to model the way the human brain processes information. One of its most distinctive features is that it "learns by experience".

That is, given a large data set and “training rules” about data relationships, the neural network can respond in novel ways to new inputs (such as data that were not used in the original “training”). The use of neural networks in clinical medicine is growing (152,153) and its use in TBI is being explored (154).

Two primary issues surround the use of neural networks in prognostication. The first is accuracy: does the use of the neural networks result in more accurate predictions than more traditional models? The evidence from other fields is mixed (152) and a study on TBI found no difference in accuracy between a neural network analysis and one based on logistic regression (154). The other issue surrounding the use of neural networks is ease of clinical use. The concern is that neural networks are “black boxes” because there is no way of making explicit how they generate their predictions. All one can know are the data inputs and the resultant outputs. In more traditional methods, the algorithm used is explicit and its conceptual bases understandable, even if its numeric aspects are not. It has been suggested that this lack of transparency would limit the use of neural networks by clinicians (153). Despite these concerns, the use of neural networks in outcome prediction after TBI holds promise and bears further investigation. Other statistical methods are also being evaluated; readers are directed elsewhere for more information (155,156).

### CONCLUSIONS: SUGGESTIONS FOR FURTHER RESEARCH

There is still much work that needs to be done on prognosis after traumatic brain injury. For one, it would be helpful if a larger group, such as a task force, reviewed the literature in order to see if they could replicate the results of this chapter. Having a group of individuals involved, rather than a single author, might improve the quality of the criteria used, the scope of the literature search, as well as the classification of the studies. In addition, a larger group could expand the grading system that is used to include different levels of strength of evidence (as is common in most evidence based reviews). At the time of this writing, it appears that the American Congress of Rehabilitation Medicine has assembled a task force that may pursue these goals.

In addition to reviewing already existing studies, it is important that more studies be conducted in an attempt to confirm the findings of this review. However, these studies should be designed so as to build on the strengths of the current literature and to compensate for its weaknesses (in scope or design). This is crucial given how few studies formed the basis of the recommendations presented here. Most generally, it would be important for future studies to incorporate the concept of threshold

values to maximize their clinical utility. It would also be important to focus on those variables that have already shown promise as being clinically useful (such as the duration of coma or PTA, magnetic resonance spectroscopy, etc.) rather than those that are clearly not powerful enough to aid in clinical prognostication (such as initial GCS or CT imaging). It is noted that the utility of neuropsychological testing is still unclear, given the limitations of the studies done to date. It would be useful to have better studies in this area to determine the value of such testing.

In addition to selecting appropriate variables, it would be important for future studies to address shortcomings in the outcome measures used previously as well as to study more relevant populations. With regard to outcome measures, given the clear limitations of the Glasgow Outcome Scale, more studies should be conducted with newer, more promising measures such as the Community Integration Questionnaire. The duration of follow up should be longer as well, given what is now known about the possibility of clinically meaningful recovery that can occur a year or more after an injury. In terms of setting, more studies are needed that are based in inpatient rehabilitation (thus circumventing the problems that arise when attempting to extrapolate from the acute care setting to patients in rehabilitation).

Finally, it is important that studies be conducted that attempt to identify what types of prognostic information patients and families want. There have been very few studies that have explicitly addressed this issue (see the discussion in Appendix II). Yet, because prognostication is ultimately a *clinical* act (one directed at and meant to benefit patients and families), it is crucial that future studies on prognostication (as opposed to studies on outcomes more generally) be designed around the explicit needs of patients and their families.

### APPENDIX I: EVALUATING AN ARTICLE ON PROGNOSIS

This section discusses some general guidelines that readers can use when evaluating individual studies on prognosis; these are summarized in Figure 14-11. Interested readers are referred to more detailed discussions of these issues (157–165). In general, three main principles guide the critical evaluation of an article on prognosis: the *quality* of the study, its *relevance* to one’s own practice, and the *utility* of the findings. A study can be methodologically sound but inapplicable to one’s practice, for instance if the study population is not similar to one’s own. Or the reverse can happen: the study is relevant to one’s practice but, because of problems in design, one cannot rely on the study’s results. Finally, a relevant and methodologically sound study may still not be helpful because

<p><b>Outcomes</b></p> <ul style="list-style-type: none"> <li>• Is the outcome clinically important?</li> <li>• Is the outcome measure validated?</li> <li>• Is the outcome measure described well enough that it can be easily applied?</li> <li>• Did an appropriate amount of time elapse before the outcome was measured?</li> </ul> <p><b>Predictor Variables</b></p> <ul style="list-style-type: none"> <li>• Are the predictor variables described well enough that they can be easily applied?</li> <li>• Are the predictor variables easily accessible?</li> <li>• Do the predictor variables have high reliability?</li> </ul> <p><b>Sample</b></p> <ul style="list-style-type: none"> <li>• Is the population described well enough to determine if they are similar in relevant aspects to your own (including the site)?</li> <li>• Was there any bias in the selection of subjects (for instance, an inception cohort vs. a convenience sample)?</li> <li>• Was the sample large enough?</li> <li>• Was there minimal loss to follow up?</li> <li>• Were the characteristics of those who were lost to follow up compared to those who completed the study?</li> </ul> <p><b>Results</b></p> <ul style="list-style-type: none"> <li>• Were the findings reported in a form that is useful for clinicians (e.g. absolute risk)?</li> <li>• Was the precision of the estimates provided (e.g. confidence intervals)?</li> <li>• Was there an evaluation of validity (replication of findings in same sample)?</li> <li>• Have the findings been confirmed in other studies (reproducibility)?</li> <li>• Are the findings believable on biological grounds?</li> <li>• Do the findings represent an advance over already available prognostic tools?</li> </ul>
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**FIGURE 14-11**

Guidelines for Reading an Article on Prognosis

the results are reported in a way that makes it difficult to apply to clinical practice.

These principles of quality, relevance, and utility guide the questions that one should ask about the various components of the study: outcomes, predictors, sample, and results (Figure 14-11). It is also important to assess the statistical analysis performed, although this issue is only briefly addressed here. Many of the criteria listed in Figure 14-11 will be familiar: they are identical to the inclusion criteria for this review. The second appendix provides a detailed review of these criteria; therefore, they will not be discussed here. Rather, the focus will be on the new criteria listed. The following discussion is organized according to the topics mentioned earlier (outcomes, predictors, sample, results).

## Outcomes

The outcomes must be of clinical relevance, one that would matter either to the clinician, the patient, or their family. Whatever outcome measure is used, it should be well described so clinicians can apply it to their own patients. The outcome should also be easy to measure in clinical practice. It should also be a measure that has either already been validated or, at least, has had some assessment of validity performed in the study itself. Finally, the outcome should be measured at an appropriate time (at least 6 months after a TBI).

## Predictors

Many of the same criteria apply to the study's choice of predictor variables: they should be well described, have high reliability, and be easily accessible or easily performed by the clinician.

## Sample

The sample should also be well described, so readers can decide if the subjects are similar to their own patients. In assessing this, it is also important to keep in mind the nature of the treatments received by the study population and whether one's own patients receive similar treatments. The study should be prospective, utilizing an inception cohort, rather than retrospective (e.g., a case-control design). The sample size should also be adequate. The size of the sample not only affects the precision of the estimates (e.g., the width of the confidence intervals) but also ensures the sample obtained is representative of the population. In addition, many of the statistical analyses performed require a sample of a certain size for the results to be valid (e.g., for multivariate analyses).

There should also be minimal loss to follow-up. Although most authors recommend the loss to follow-up should be no greater than 15–20 percent, the real issue is the number of people lost to follow-up relative to the number of people with the outcome of interest. One way of evaluating this would be to examine what would happen if everyone lost to follow-up ended up in each of the outcome categories. For instance, a 15 percent loss to follow-up in which the outcome categories were equally likely (e.g., 50 percent “good” and 50 percent “bad”) would not affect the results significantly. Even if you assume that all of those lost to follow-up either had a good outcome or a bad outcome, the percentages would shift only slightly (e.g., to 57 percent and 43 percent in either direction), not enough to affect prognostication. On the other hand, in a study in which no one achieved a certain outcome (e.g., severe disability), a 15 percent loss to follow-up would be significant if all 15 percent were severely disabled. Finally, it would be ideal if the

characteristics of those lost to follow-up were compared with those who remained in the study.

## Results

The results have to be reported in a way that is clinically useful, so they can be used to formulate a prognosis for individual patients. In general, absolute risks or simple percentages are more useful than measures such as relative risk, likelihood ratios, odds, etc. There should also be some report of the precision of the estimate provided (e.g., the width of the confidence interval). Ideally, there should also be some assessment of the model's validity: both by replication of the findings in the original sample as well as, more importantly, replication at other sites. Although this assessment of validity represents the ideal, it is rarely met in studies of TBI. An exception that illustrates the importance of replication was a study done in the acute care setting (166). This study applied a previously published model (167) to their own patient population. Although the model was reported to be 100 percent accurate in the original study, the second study found it to be only about 65 percent accurate in their patient population.

Finally, the results of the study should be interpreted in the larger context of the available literature. Do the findings make sense based on what is known of the pathophysiology and natural history of TBI? Have other studies confirmed the findings? Do the findings provide for more accurate prognoses than is already possible?

## APPENDIX II: METHODOLOGY

### Methods

Extensive literature searches (based on the inclusion criteria described below) were performed on Medline, PsycInfo, and the personal database of a colleague of the author (which has over 20,000 TBI specific articles); the search covered the period from 1983 through 2004. Hundreds of articles were retrieved and their bibliographies then reviewed for further references. All the articles were then reviewed to determine whether they met the inclusion criteria. The inclusion criteria were developed after extensive discussions with various professionals (including, for instance, neurosurgeons and biostatisticians), as well as family members and survivors. The general principles that guided the selection of the inclusion criteria are presented in Figure 14-4. The inclusion criteria themselves are listed in Figure 14-5. The sections that follow explain the rationale for the criteria chosen.

### Population

*Severe TBI* Patients with moderate and, especially, severe TBI make up most of those admitted to inpatient

rehabilitation. Therefore, the original plan was to focus on both of these groups. However, there were no studies meeting the inclusion criteria that focused only on moderate TBI. Even among the studies that met the inclusion criteria, only a few included patients with moderate injuries and, even then, they only comprised a small percentage of the total number of patients. Moreover, these studies had other eligibility criteria that excluded many of the moderately injured patients (e.g., by only including patients who had been admitted to an ICU). For these reasons, this chapter focuses on patients with severe TBI. This seems appropriate given the limited evidence available for patients with moderate injuries, the generally good outcomes in this group (10), and because patients with severe injuries are the ones for whom prognostication is often the most difficult. Studies on civilian penetrating brain injury were evaluated separately from those on closed brain injury, given the substantial differences between these two populations.

*Subacute Period After TBI (Acute Care and Rehabilitation)* The focus of this chapter is on prognostication during the subacute period, which was defined as the period from the initial stabilization of the patient after the injury (usually in the first week) to approximately three months after the injury. It was felt that this period was of most concern to rehabilitation clinicians working with TBI. Certainly, there are other periods in which the question of prognosis is relevant. Most obviously, there is a great deal of concern about prognosis in the acute setting, early after a TBI. Similarly, survivors and family members often continue to have questions about "final" recovery many months or even years after a brain injury, during the chronic phase.

In this chapter, however, the focus is on prognostication during the time that lies between these two periods. There are various reasons for this focus. For one, the literature on prognostication is enormous, and it would be impossible to survey all of it in a single chapter. Besides, at least with regard to prognostication in the acute stage, there has already been a comprehensive evidence-based review (168). In addition, the focus in the immediate aftermath of a TBI is mostly on mortality rather than on broader outcomes. Rehabilitation professionals are less likely to be involved during the period immediately after the injury, although they often play a more important role after the patient is stabilized. Although rehabilitationists are the primary clinicians during the chronic phase (after approximately 6–12 months), the questions that arise during this period are often easier to answer because much more information is available by then.

In contrast, there is relatively little information during the subacute period, which is one reason why prognostication is so difficult then. At the same time, the need for prognostic information is greatest during this period.



Families have often been so focused on issues of survival during the acute care stage that they are just beginning to think about the long-term implications of the injury. This is especially true after patients are admitted to inpatient rehabilitation. In many ways, then, this period represents a pivotal point after a TBI and providing information about outcomes is one of the clinician's most important obligations during this time (2).

The question then arose as to whether to limit the review to only those studies done in the inpatient rehabilitation setting or to also include studies done in acute care. The populations are clearly different. The primary issue is that only a subset of all TBI patients admitted to acute care eventually goes to inpatient rehabilitation. Many patients die in the acute care setting. Of those patients that survive, some have improved to the point that they do not require inpatient rehabilitation and can be discharged with outpatient services. At the other end of the spectrum, many survivors of TBI have not made enough neurological progress to meet the criteria for admission to inpatient rehabilitation and are therefore often discharged to long-term care facilities or home. Thus, there is a concern that the acute care population would not necessarily be representative of patients seen in rehabilitation.

Despite these concerns, studies done in the acute care setting were included in this review. Since both acute care and inpatient rehabilitation usually occur during the subacute time period, it was felt that studies from both settings were needed to adequately represent this phase. Also, rehabilitation professionals often first encounter patients in the acute care setting and are often asked by other clinicians or family members about long-term prognosis early after a TBI. Additionally, despite differences between the two populations, the variables affecting prognosis seem to be similar; in fact, there were no appreciable differences in the findings of the studies done in the two settings.

The most important reason for including the acute care studies, however, is that there were only five studies conducted in the inpatient rehabilitation setting that met the inclusion criteria. Given the limited number of well designed rehabilitation studies, the choice was either to include acute care studies or to liberalize the inclusion criteria so more studies based in rehabilitation could be included. It was decided that well designed studies of prognosis from the acute care setting would be more useful than methodologically weaker studies based in the rehabilitation setting.

*Studies Published After 1983* Beginning in the early eighties, changes in pre-hospital, neurosurgical, and ICU care have resulted in a steady decline in mortality from TBI (169–171). Whether functional outcome has also improved is less clear. There has been some concern that

although mortality has declined, the survivors are disproportionately severely disabled. Recent reports don't support these fears, however, and it now appears that functional outcomes have improved along with survival (172,173). Because of these changes in care, it was decided to exclude studies published before 1984, under the assumption that the care patients received before that time differed from current care in ways that directly impact outcome. Specifically, it is assumed that studies done before the early eighties would underestimate survival and function. Although acute medical and surgical care continued to improve after the early eighties, most of these changes have been relatively minor compared with those of twenty years ago. The primary changes over the past fifteen years have been the adoption of the new standards by an increasing number of non-academic centers (170,173).

*Setting: North America/Western Europe/Australia/New Zealand/Israel* Although there is some documented variation in TBI care *within* the United States (as well as between the U.S. and Europe) (174), care in the countries listed above was similar enough to justify grouping them together (175). Even though care in the excluded countries may be similar to that in the countries above, there is no evidence to support this. Because variations in care are likely to affect outcomes, studies originating in countries other than those listed were excluded.

*Age: Adult* Since pediatric TBI is discussed elsewhere the studies included in this review focused exclusively or predominately on *adult* TBI. Also, because age is such a powerful predictor of outcome, also included were studies on the elderly.

*Subpopulations* In general, studies that included a wide range of patients were preferred, since this would most closely resemble the typical patient population seen by most rehabilitation clinicians. In addition, beyond a certain point, it becomes difficult for clinicians to use a different set of guidelines for minor variations in pre-injury, injury, or post-injury factors. Some groups are so distinctive, however, that studies that focused exclusively on them were included. The most notable examples in this review were the studies on the elderly and those with civilian penetrating injuries. A few studies that focused on other subsets of the TBI population were included only if that subset made conceptual sense and was easily identifiable by a rehabilitation professional. For instance, included were studies that limited themselves to patients who regained consciousness in acute care as well as one that focused on TBI patients who did not sustain other injuries. However, studies that focused only on those patients with, for example, traumatic subarachnoid hemorrhage or a history of elevated intracranial pressure,

were excluded under the assumption that this information was often not readily available and did not reflect conceptual categories that rehabilitation professionals routinely use.

### Predictor Variables

The review is limited to the following predictor variables: age, initial Glasgow Coma Scale score (GCS), length of coma (LOC), duration of post-traumatic amnesia (PTA), and early neuroimaging (CT and MRI). There are several reasons for focusing exclusively on these predictors. First, these variables are among the most powerful predictors of outcome available. More importantly, they represent pieces of information that are either easily available to most rehabilitation clinicians (e.g., age, initial GCS, etc.) or can be prospectively determined in the rehabilitation setting (e.g., duration of PTA). Although there are other variables that can also have a significant impact on outcome (e.g., pupillary abnormalities, hypoxia, premorbid functioning, etc.), this information is often not readily available (for instance, because of the limited availability of medical records). Thus, studies that rely on utilizing this information may not be particularly useful for rehabilitation clinicians providing subacute prognostication.

Only those studies that used the *total* GCS score were included. Although there are compelling reasons for the use of just the motor score in prognostication (176), rehabilitation clinicians do not often have available to them a patient's GCS subscores. There were also many studies that combined the variables selected for this review with other variables to create a single predictive model (for instance: age, pupillary abnormalities, and GCS motor response). Although the clinical utility of these models is dependent on the *combination* of variables (some of which are not readily available to the rehabilitation clinician), the studies making use of these models were included because they provided evidence that the variable of interest (e.g., age in the example above) was, after a multivariate analysis, associated with outcome.

Although neuropsychological testing during inpatient rehabilitation was originally included as a predictor of interest, none of the studies on early neuropsychological testing met the methodological criteria. Although not discussed as part of the evidence based review, the studies that have been done are briefly reviewed in the body of the chapter.

### Outcomes

*Outcome Measures* One of the central issues in prognostication is to be clear about the outcome of interest. There are many outcome measures available: survival, physical impairment, ability to perform activities of daily living, cognitive and behavioral status, return to work,

independent living, quality of life, etc. (177,178). The outcome one chooses depends on the question(s) one is asking and whether these questions are being asked for research or clinical purposes. In particular, the interests of professionals (especially researchers) and families do not always coincide. For instance, there is evidence that the outcomes of most interest to family members, at least during the rehabilitation phase, have to do with broad conceptual categories such as independent living and return to work (179,180). Besides the intrinsic importance of these categories, there is a symbolic importance associated with them (181). That is, given the importance our culture places on employment and independent living, these roles come to symbolize our membership in the community at large. Even the concern with other outcomes (e.g., physical impairment, cognitive decline, etc.) is interpreted mainly by their impact on these more holistic functional categories (179,180).

Unfortunately, most studies do not use measures of these types of outcomes, for several different reasons. First, these outcomes are so broad that they can include a wide range of patients within a single category. For instance, the category of severe disability in the GOS would include both a minimally conscious patient as well as someone independent in basic activities of daily living who is unable to live alone because of cognitive deficits (182). These measures are also insensitive to changes that can occur beyond the first 6 months to a year, making them less useful in studying the longer term natural history of TBI (178,183). Third, the psychometric properties of these global outcome measures often are not as good as those of more fine-grained research measures. For example, there are concerns about inter-observer agreement in the clinical use of the GOS (15). Another concern with the GOS is the fact that what is documented is the rater's subjective impression of a person's abilities rather than actual outcome. For instance, the measure documents the rater's beliefs about a person's ability to work rather than actual employment (which may account for the finding that ratings on the GOS may not be as strongly correlated with measures of employment as one would expect) (177).

The broadness of categories such as return to work or independent living can obscure the underlying mechanisms that mediate the outcome. Although this is sometimes seen as an advantage of these measures (so that they "integrate" the effect of many deficits into a final outcome such as work) (184), this characteristic can also lead to the loss of valuable information. For instance, is the person unable to live independently because of executive dysfunction, impulsivity, or physical impairment? Or because of factors that have nothing to do with the brain injury (e.g., other disabling physical conditions, financial resources, family support, etc.) (25)? By collapsing these distinctions, the use of these outcome measures can obscure the underlying deficits that

actually prevent people from living independently or returning to work.

There is also evidence that, at least early on, both patients and family members overestimate the contribution of certain outcomes to eventual quality of life (such as independent living) and underestimate the importance of others (such as social relationships). During the chronic phase of TBI, most studies show that emotional and behavioral issues are far more important to family members than, for instance, residence or occupational status (180,185–187). Even for patients, there is evidence the GOS categories do not correlate well with their own ratings of their quality of life (90). The broad categories of return to work, independent living, or the GOS are simply not designed to identify sequelae such as quality of life, social relationships, behavioral disturbances, etc.

However, although they will likely change their minds later, the fact remains that it is still these broad categories of functional outcome that families and patients are concerned with during the subacute period. To prognosticate about outcomes that are not yet relevant to them can lead to dissatisfaction and the perception that their needs for information are not being met. And since prognosis is ultimately a clinical act that tries to address the *current* needs of families and patients, their preferences have to be considered. For this reason, this review was limited to those studies that focused on return to work or independent living, either directly or through the GOS.

Despite its other limitations, the GOS actually seems to be one of the most useful measures of these sorts of outcomes. This is because the GOS utilizes outcome categories that correspond to those used by lay people, making results expressed in terms of its categories useful to clinicians. For instance, in discussing that their loved one will likely be “moderately disabled” in a year, the clinician can explain that the patient will likely be able to live independently but will have residual deficits precluding their being able to return to competitive employment. This outcome is understandable to family members since they, too, think in terms of independent living or employment.

In this respect, the GOS contrasts to measures such as the Disability Rating Scale (DRS) that either report a numerical score that has no real meaning to a layperson or is divided into categories (e.g., partial disability, moderately severe disability, etc.) that also have no clear conceptual correlates. Although it is true that information about living situation and employment can be extracted from the DRS, the data needed to do so is rarely reported in the literature (it is usually only the total score that is reported). The relatively clear meaning of the GOS categories is also an advantage relative to the results of neuropsychological testing. For most family members, a decline on a neuropsychological test is of little relevance except as it has an impact on “real-world” outcomes such as independent living.

Despite its advantages in addressing the needs of patients and families, there are still the many methodological limitations of the GOS mentioned earlier. There are newer measures that retain many of the advantages of the GOS while avoiding some of its limitations (e.g., the Community Integration Questionnaire). Unfortunately, there were no studies using these measures that also met all the other inclusion criteria. This fact reflects one of the primary reasons for the use of the GOS in this review. Because it is the most widely used measure in the TBI outcomes literature, including the GOS as an outcome measure significantly expanded the number of studies that could be included in this review. In fact, to exclude studies that used the GOS would have limited this review to less than a handful of studies (that met all the other criteria listed).

*Outcome Measured at 6 Months or Later* For several reasons, this review is limited to studies that assess outcome no earlier than six months after injury. Waiting *at least* six months is uncontroversial given the well-known clinical observation that, for most individuals, significant improvement occurs during the first six months after an injury. It could be argued, however, that since recovery clearly continues after six months, it would be better to wait a longer period of time, for instance, at least a year. Indeed, there is growing evidence that some individuals can continue to have meaningful recovery even many years after their injury (188–190). Nonetheless, there are compelling reasons to include studies that assess outcome as early as six months. First, studies have shown that, despite continued improvement, it was rare for an individual’s GOS category to improve after six months (191). More practically, if only studies that assessed outcome beyond six months were included, well over half of the studies would have been excluded, further limiting what is already a small evidence base.

### Methodological Criteria

The methodological criteria adopted are, for the most part, self-explanatory. The review is limited to studies with consecutive admissions (or a random sample of consecutive admissions) to minimize the possibility of systemic bias (which might arise from sampling based on any other criteria). Likewise, the requirement of at least 80 percent follow-up minimizes the biases that might be encountered with high rates of drop-out. Historically, TBI outcome studies have been characterized by high rates of loss to follow-up (1/3 to 1/2 of the original sample); the implications of this for the validity of studies on outcome have been recently reviewed (192). Unfortunately, almost no studies analyzed the characteristics of those lost to follow-up to see if they differed substantially from those who were included. In the interest of having more than

1–2 studies to review, it was decided that an analysis of patients lost to follow-up would not be required of studies to be included.

The criterion specifying a minimum sample size was adopted from the AANS acute care prognostication review (168). Finally, the studies were reviewed to ensure that some form of statistical analysis was performed on the data of interest. If not, the study was still included if enough information was provided for the statistical analysis to be done by a knowledgeable reader. This was an issue for some of the older studies, where the distribution of outcomes was occasionally reported only in a descriptive manner. However, there was no attempt to screen studies based on the statistical models employed. The most commonly utilized models in this area are regression models and decision trees. The features and limitations of these approaches are detailed elsewhere (193–200).

There are some potential criteria not utilized in this review, either because they were not applicable or because they would have greatly limited the number of studies available. Most notably, a study was included even if it did not adjust for confounding factors (because so few did so). However, those studies that performed an univariate versus a multivariate analysis (or something else to adjust for confounding factors) are noted in the tables. More importantly, the fact that the studies that did not adjust for confounds came to the same conclusions as those that did increases the confidence in the findings of the review.

### Threshold Values and Confidence Intervals

It cannot be automatically inferred that a particular outcome is impossible, just because no one over or under a particular threshold value had the outcome of interest in a particular study. This is because there is always a degree of statistical uncertainty, even when the outcome of interest does not occur. For example, even if no one with a duration of PTA greater than three months had a good recovery in a particular study, it might still be *statistically* possible that a certain percentage of them could have achieved that outcome. This possibility can be quantified by confidence intervals. In a study where no one had the outcome of interest, the lower end of the confidence interval would be zero, while the upper end would represent the largest number of people who could statistically be expected to develop the outcome of interest. The width of this confidence interval will depend on the sample size.

For instance, if no one out of a sample of 87 people achieved a good recovery on the GOS, the 95 percent confidence interval would be approximately 0 to 3 percent. That is, the findings are compatible (with 95 percent certainty) with up to 3 percent of that group achieving a good recovery. If, instead, no one out of a sample of only

17 people achieved a good recovery, the confidence interval would be much wider (approximately 0–16 percent). Therefore, the most that one can infer from the smaller study (with 95 percent certainty) is that anywhere from 0 to 16 percent of similar people could have had the outcome of interest. It is also important to keep in mind that a study in which no one had a particular outcome is not necessarily stronger evidence for a threshold value than a study in which some subjects had the outcome. It all depends on the width of the confidence interval. For instance, a study with a large sample (e.g., 150) that reported that 4 percent of subjects had a good recovery would actually have a smaller confidence interval (1–9 percent) than a study with a smaller sample (e.g., 27) in which no one achieved a good recovery (CI 0–11 percent).

Unfortunately, none of the studies that reported threshold values reported the associated confidence intervals. Therefore, the author calculated the confidence intervals for all the threshold values. However, only those threshold values with a 95 percent confidence interval of no greater than 0–12 percent are reported. This figure represented a balance between the limits of tolerability of error and the wish to include as many studies as possible.

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# 15

## Neuroimaging Correlates of Functional Outcome

*Erin D. Bigler*

### **NEUROIMAGING CORRELATES OF FUNCTIONAL OUTCOME**

How do neuroimaging findings best predict outcome once the brain has been injured? The answer is complicated. Even though many trauma-induced abnormalities can be identified by neuroimaging and such findings represent one of our best objective measures of brain injury, there are numerous variables (in addition to simply identifying neuroimaging abnormalities) that have to be considered. For example, imaging—even functional imaging—represents only a particular moment in time, yet predictions of outcome typically involve statistical statements of much broader timeframes involving the future, including the lifetime of the individual injured. Likewise, the recovery process is dynamic and ever changing, particularly in the first year of injury. A host of injury variables apply, including: the type of brain injury, the severity of injury, the brain regions most likely affected, the age at time of injury, as well as, the issues involving cognitive reserve and individual differences. Since the advent of contemporary neuroimaging the type, degree, location, and a host of other indicators of brain imaging abnormalities have been examined in an attempt to answer this question.

The chapter that follows will provide an update on this topic, by first offering an overview of the history of lesion-location research in predicting functional outcome

from traumatic brain injury (TBI), followed by typical injury characteristics observed in neuroimaging of TBI that are predictive of functional outcome, along with current methods for establishing the best predictor of outcome and future implications of the clinical utility of neuroimaging in evaluating functional outcome from TBI. Because of rapid changes in technology and how brain scans can be analyzed (1), only a few studies have actually systematically addressed this issue with a mixture of qualitative and quantitative analyses in using neuroimaging to predict functional outcome (2–10). Basically, these studies demonstrate that presence of abnormalities in structural imaging are associated with more negative outcome, particularly when the abnormalities are shown to be chronic. This chapter will review these studies along with other clinical associations and methods for the use of structural imaging findings in the prediction of functional outcome in TBI.

### **HISTORICAL PERSPECTIVE AND AN INTRODUCTION TO THE PROBLEMS OF PREDICTING FUNCTIONAL OUTCOME BASED ON STRUCTURAL NEUROIMAGING**

Clinical neurology, as did much of medicine, developed from a ‘signs and symptoms’ approach, where a particular neurological symptom (i.e., paralysis) had a clinical

presentation (i.e., hemiplegia) that specified a particular pathophysiology (i.e., corticospinal tract damage potentially localized), depending on what other signs and symptoms were present. The motor system analogy is used here, because it was the first to be comprehensively examined resulting in established functional outcome using lesion-localization methods of neuropathologists and clinicians. Likewise, motor impairment has been the system most extensively examined from a traditional structural as well as functional neuroimaging perspective (see Figure 15-1) (11, 12) where clinical outcome has been related to underlying brain pathology. For example, using neuroimaging techniques, identification of damage within the corticospinal tract (see Figure 15-2) typically leads to some type of motor impairment as shown in Figure 15-3; where this patient had left-side hemiplegia as a result of shear injury at the level of the internal capsule. Accordingly, knowing the location of the lesion within a dedicated neural pathway (i.e., corticospinal) for a specific function (in this case, motor) leads to a predictable functional outcome (impaired motor skills).

Extensive mapping of sensory-perceptual and some language based pathologies were the next to show lesion-location specificity and prediction of functional outcome depending on a signs and symptoms approach, particularly with primary sensory systems (13). Mapping of language function, however, turned out to be far more

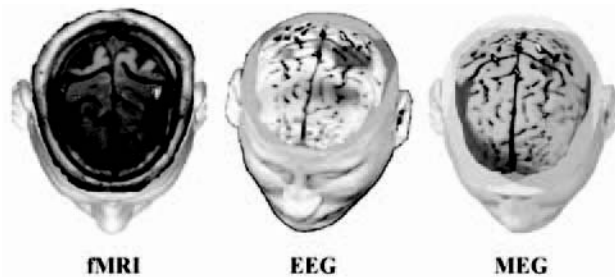


FIGURE 15-1

Three images of the cortical activation related to a simple unilateral finger movement showing how functional imaging techniques can isolate motor cortex. *Left:* The cortical regions showing an increased hemodynamic response with respect to the rest period. Such hotspots are located over the primary motor cortex. *Center:* The spatial distribution of the estimated cortical current density distribution occurring over a reconstruction of the cortex 100 ms before the movement occurs. The cortical current density distribution is obtained by high-resolution EEG recordings with 128 electrodes. *Right:* The current density distribution is relative to the same time instant (100 ms before movement) but is estimated from the MEG recordings in the same subject. This demonstrates the focal nature of somatomotor function. Used with permission from Babiloni et al. (12). Accordingly, cortical damage outside this system does not impair direct motor functions of the hand

problematic than initially anticipated in light of what were thought to be well known “language” centers of the brain such as Broca’s and Wernicke’s areas. It became apparent that language was less dedicated to precise locations that could be consistently identified between individuals and was more loosely distributed than the more ‘hard-wired’ sensory and motor systems. So, instead of showing discrete lesions that consistently impaired language, studies generally found more extensive regions wherein damage anywhere within some boundary would result in language impairment. This is nicely demonstrated in Figure 15-4 taken from the work of Bates et al. (14), mapping out left-hemisphere lesions in right handed individuals that produce language impairment (deficits in word fluency and auditory comprehension). Figure 15-4 also shows that no uniform area that when damaged produced the same disturbance in language in all subjects, but rather damage across a broad range of the left hemisphere resulted in impaired language function. There were areas where the likelihood of language impairment was maximized, but this illustration also demonstrates individual differences in brain organization once outside of primary motor and sensory systems. The more distinct 1:1 correspondence between pathology and

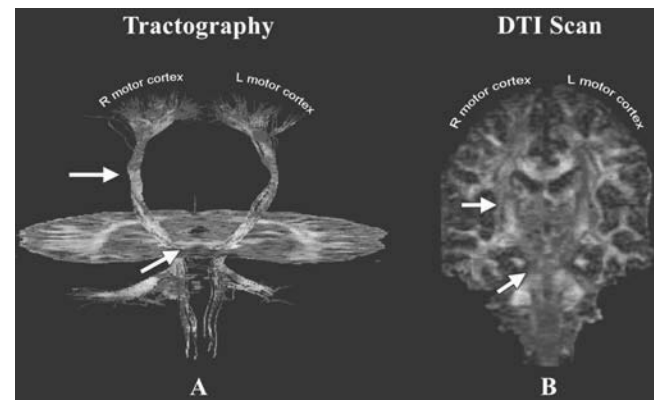


FIGURE 15-2

(Left, A) Diffusion tensor imaging (DTI) tractography is used to isolate the corticospinal tract (upper arrow), demonstrating its descent from motor cortex, down through the midbrain region (lower arrow). Arrows represent where injuries to this direct motor pathway resulted in the motor impairment and paralysis seen in the case presented in Figures 15-3 and 15-6. Although the fibers that comprise the corticospinal tract involve only a very small region of the brain, damage anywhere along this pathway will result in some type of functional impairment in motor abilities. (Right, B) Colorized DTI scan image in coronal plane used to identify tract orientation used to perform the tractography to isolate the corticospinal tracks. Blue represents tissue aligned in vertical orientation which was the source to extract the fiber pathways depicted in A. Adapted from Lazar et al. (22) and Lainhart et al. (118) used with permission

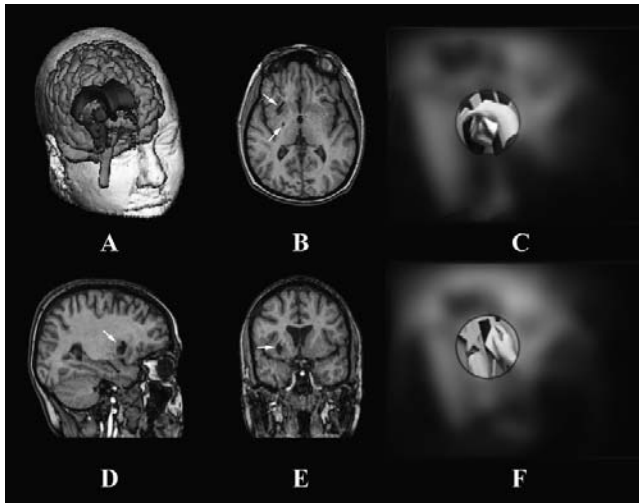


FIGURE 15-3

MR imaging showing residual small, focal shear lesions involving the basal ganglia (arrows in B, D, and E) and internal capsule (B, bottom arrow) in the right hemisphere (scans are in radiological perspective, with right on the viewer's left) that result in impaired motor function on the left side of the body (refer to C). In F, the patient has no difficulty placing blocks while blindfolded to successfully complete the Tactual Performance Test. In contrast, impaired motor performance is present in the left hand demonstrated by paralysis and posturing as shown in C. This figure demonstrates the impact of a strategically placed lesion (shown in red in A) to result in functional impairment. B, D and E represent the axial, sagittal and coronal views with arrows pointing to the focal lesions. The figure in A contains the 3-D reconstruction of the brain with the ventricle in blue, showing the location of the focal damage. Figure 15-6 (also from this patient) demonstrates atrophy of the cerebral peduncle, a consequence of damage to the corticospinal track and some focal hemorrhaging (petechial in nature) that occurred at the level of the midbrain

function as found in dedicated motor and sensory systems is less apparent once function is defined by some element of cognition or behavior. In general, widely dispersed neural regulatory systems underlie complex behaviors and therefore, structure-function relationships predictive of functional outcome outside of primary motor and sensory deficits are more difficult to establish (15). Nonetheless, general statements can be made about neuroimaging defined damage to certain brain regions or neuroregulatory centers and functional outcome.

Also, because of neural mechanisms that relate to recovery and adaptation, small lesions strategically placed within dedicated neural pathways may have pronounced effects upon functional outcome of motor or sensory abilities, such as complete paralysis, blindness or loss of smell or auditory processing. In contrast, extensive lesions that do not damage such dedicated primary systems may have no or minimal effect upon such functions, even though the

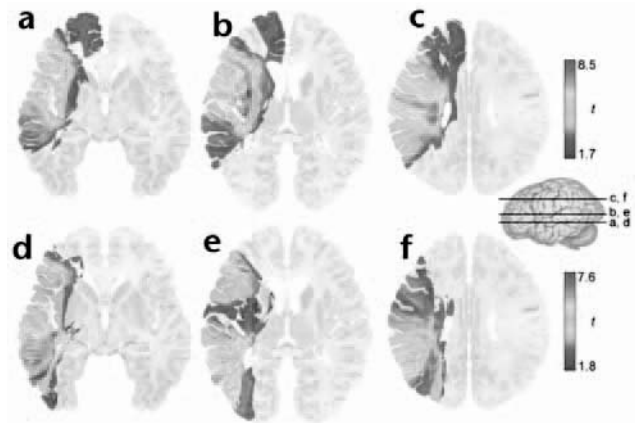


FIGURE 15-4

This illustration demonstrates the dispersion of left hemisphere regions that disrupt language function after a focal cerebrovascular accident. Representative slices from voxel-based lesion-symptom mapping (VLSM) computed for fluency and auditory comprehension performance of 101 aphasic stroke patients. These maps are colorized depictions of *t*-test results evaluating patient performance on a voxel-by-voxel basis. Patients with lesions in a given voxel were compared to those without lesions in that voxel on measures of fluency (a-c) or auditory comprehension (d-f). High *t*-scores (red) indicate that lesions to these voxels have a highly significant effect on behavior. Dark blue voxels indicate regions where the presence of a lesion had relatively little impact on the behavioral measure. Only voxels that were significant at  $p = 0.05$  (controlling the expected proportion of false positive) are shown. Insert of brain depicts the level of each slice. Lesions within the insula (b) and deep parietal white matter (c) had the most impact on fluency, whereas injury to the middle temporal gyrus (d) produced the largest effect on measures of auditory comprehension. Used with permission from Bates et al. (14)

area of damage may encroach such regions. This is readily observed by comparing the case presented in Figure 15-3 to the one in Figure 15-5. In Figure 15-3 and in the additional imaging presented in Figure 15-6 the patient has distinct damage at the level of the internal capsule and basal ganglia on the right, as well as Wallerian degeneration at the level of the cerebral peduncle, reflective of generalized 'downstream' wasting of the corticospinal track. This is consistent with the left side motor involvement as shown in Figure 15-3. In contrast, the patient shown in Figure 15-5 received extensive focal damage to the left frontal region, which extends back towards motor cortex, but does not specifically involve motor systems, even though there is a small white matter (WM) lesion noted at the top of the internal capsule (see Figure 15-6). This patient had no motor deficits on a widespread neuropsychological battery of motor tasks, including the Tactual Performance Test on which the case in Figure 15-3 displayed distinct impairment. Additionally, even though there is extensive frontal

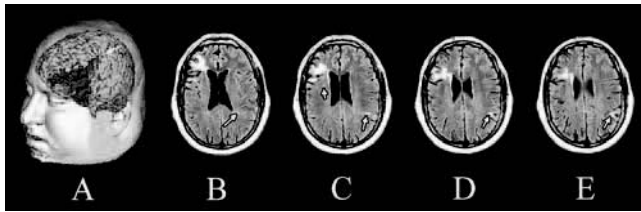


FIGURE 15-5

This case demonstrates extensive focal frontal pathology that resulted from a fall, that included frontal skull fracture and subdural hematoma that was surgically removed. Red represents the residuals from the coup injury or point of initial impact producing focal damage shown in the 3-D in A. Extensive frontal involvement is also depicted in the axial fluid attenuated inversion recovery images (FLAIR) images, but not only is the brain damaged in the region where focal impact occurred, but is damaged in a linear fashion directly opposite the point of focal impact, representing the contre coup injury as shown by the arrows. Unlike the case in Figures 15-3 and 15-6, this patient did not have paralysis, even though the focal frontal damage is very close to motor cortex (colored in green). Thus, extensive damage can occur to the cerebral cortex without causing functional impairment in motor function. Likewise, even though this patient had extensive left hemisphere damage, language function recovered to the point where he performed within normal limits, although probably below pre-morbid levels, even though some areas of damage overlap with the brain regions delimited in Figure 15-4 that would be expected to affect language

wasting in the patient presented in Figure 15-5, the patient had only minimal language deficits, despite considerable overlap of damage to frontal tissue that usually impairs language (see Figure 15-4). Other than subtly reduced word fluency and an occasional stuttering-like episode during conversational speech, the patient's performance on language tests was otherwise within normal limits.

Thus in attempting to predict functional outcome, a strategically placed lesion, albeit relatively small, may produce a distinct deficit if it involves a primary motor or sensory region of the brain. Oppositely, even large lesions such as that depicted in Figure 15-5 may not produce a consistent syndrome when damage is outside primary motor and sensory systems, due to individual differences in brain structure-function relationships. Neuroimaging methods have improved greatly over the last 20 years providing excellent macroscopic detection of brain pathology associated with TBI. As might be expected from the discussion in this section, while there are some generalities that can be established using lesion detection and localization methods to prognosticate about functional outcome (see Refs. 16, 17), there are also limitations when structural imaging is the only method used for predicting functional outcome.

Because contemporary magnetic resonance (MR) imaging so nicely depicts gross structural pathology, early neuroimaging studies were overly optimistic and assumed

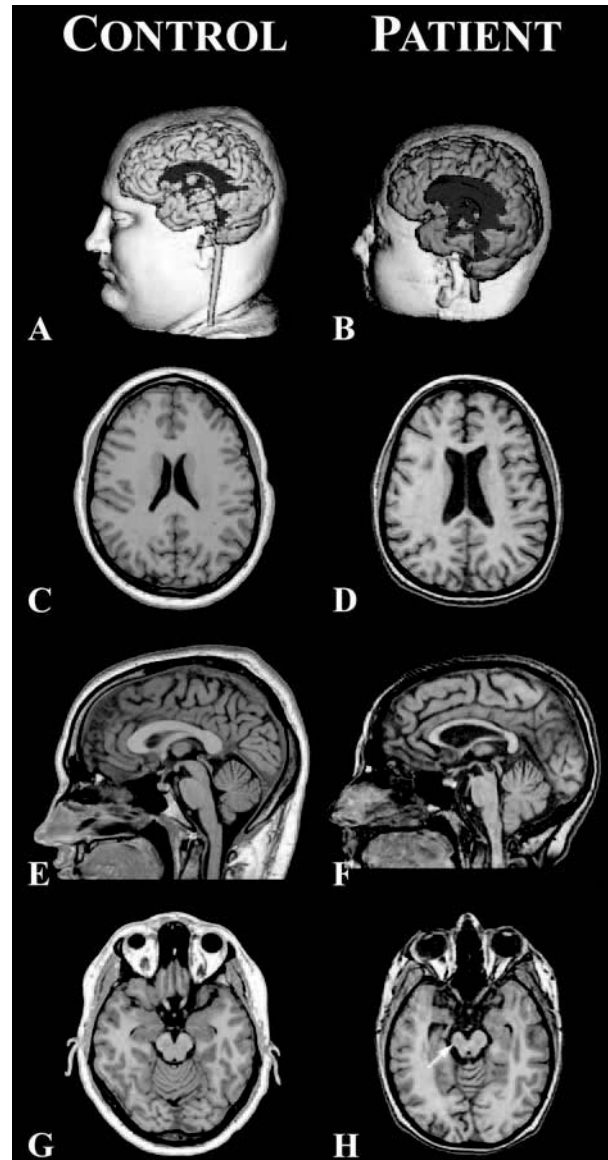


FIGURE 15-6

This is the same patient (shown on the right) as depicted in Figure 15-3, but with additional views compared to a non-brain injured control subject on the left. The axial view at the level of the body of the ventricle demonstrates ventricular dilation as a result of hydrocephalus ex vacuo. This is also a reflection of generalized cerebral atrophy, which is also demonstrated by the nonspecific loss in size of the corpus callosum (CC) as shown in F. Uniform CC reduction, as seen in this case, probably reflects uniform reduction of white matter pathways in the brain following severe TBI. In H, the cerebral peduncle on the right (viewer's left) shows atrophy, an indication of corticospinal involvement and consistent with the motor impairment shown in Figure 15-3. Also, at this level note the dilation of the temporal horns of the lateral ventricle, typically an indication of temporal lobe damage as well (see Bigler et al., Ref. 86). The 3-D image at the top shows the brain in flesh tone and the ventricle in blue. Clearly there is generalized ventricular dilation in the TBI patient as seen in B

that distinct lesion-behavior connections could be established, relating the presence of certain lesions with a typical functional outcome (see Ref. 18). However, initial studies were disappointing in their ability to predict outcome from TBI. As imaging technology improved, part of the reason for these disappointing findings became obvious, because what constitutes a 'lesion' depends on the imaging methods used and their resolution to detect abnormalities, as well as the underlying diffuse nature of TBI even when the only clinically identifiable abnormality is a focal lesion. This problem is shown in the case illustrated in Figures 15-3 and 15-6. Although distinctly focal lesions are clearly identified, generalized cerebral atrophy is also present and manifested by ventricular enlargement, wasting of the corpus callosum, and prominence of the cortical sulci. Thus, whatever effects occur from the focal injuries, do so within the backdrop of generalized damages.

From the perspective of actually detecting an abnormality with MR imaging, different MR weightings have different sensitivity in detecting pathology, which then influences how imaging findings relate to functional outcome. The problem of differences in sensitivity in detecting abnormalities and their relationship to functional outcome is presented in Figure 15-7. In this figure what shows up as an abnormality changes as to the type of MR image sequence used. For example, the T1 image provides excellent anatomical detail along with clearly defined areas of abnormal signal depicting multiple regions of damaged tissue, including prominent areas of encephalomalacia together with cystic formations in the frontal region. Although on initial review this may seem to capture the extent of the underlying damage, other imaging sequences

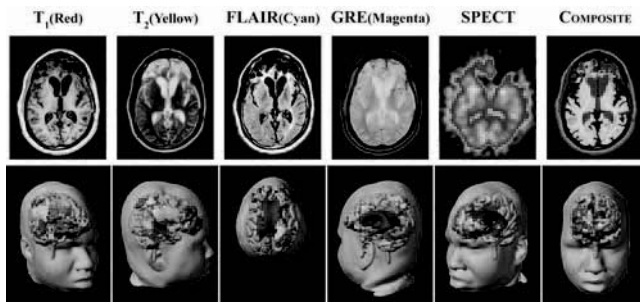


FIGURE 15-7

Multiple imaging sequences were performed on this subject with severe TBI, showing how each imaging sequences is sensitive to different types of pathology. In each case, the additional identification of abnormal signal from the separate imaging sequences has been superimposed upon a 3-D reconstruction of the brain. The ventricle is represented by blue. At the top of each figure is the image sequence (i.e., T1) and the colorization (i.e., red) depicting damage identified. Quantitative data demonstrating widespread atrophy is provided in Table 15-1

**TABLE 15-1**  
*Quantitative Analysis Comparing the Volumes of Different Brain Structures from a TBI\* Patient to a Control*

BRAIN MEASURE	TBI PATIENT	CONTROL
<b>Whole brain (cc)</b>		
Total cerebral spinal fluid	476.20	84.75
Total gray matter	635.04	886.70
Total white matter	224.22	386.60
Total temporal horn	7.54	0.71
Total lateral ventricles	75.54	17.20
Total third ventricle	4.29	0.77
Total fourth ventricle	3.41	3.13
Total ventricle	90.78	21.81
Total brain matter volume	859.26	1273.30
Ventricle to brain ratio	10.57	1.71
Total intracranial volume	1335.47	1358.05
<b>Whole cerebellum (cc)</b>		
Total gray matter	94.70	121.56
Total white matter	19.03	34.46
Total volume	113.72	156.02
<b>Frontal lobe (cc)</b>		
Dorso-lateral frontal grey and white matter total	16.13	55.66
Medio-lateral frontal grey and white matter total	34.26	81.02
Inferior orbital frontal grey and white matter total	1.85	7.51
Total csf	57.87	9.98
Total prefrontal grey matter	38.72	94.07
Total prefrontal white matter	13.53	50.13
<b>Temporal lobe (cc)</b>		
Total hippocampus	1.88	4.62
Total parahippocampal gyrus	4.57	7.07
Total fusiform gyrus	5.22	7.86
Total inferior temporal gyrus	6.19	13.36
Total middle temporal gyrus	9.77	14.49
Total superior temporal gyrus	14.03	24.79
Total temporal horn	5.59	0.72
Total gyri	41.66	72.19
Total sulci	11.33	3.48
<b>Temporal poles (cc)</b>		
Total gray matter	31.18	54.29
Total white matter	3.31	11.50
Total temporal pole	34.49	65.79
<b>Basal ganglia (cc)</b>		
Total caudate	3.58	7.76
Total putamen	4.04	10.05
Total globus pallidus	1.21	2.16
Total basal ganglia	8.83	19.97
<b>Corpus callosum (mm<sup>2</sup>)</b>		
Corpus callosum total	4.79	8.78
<b>Brain stem (cc)</b>		
Cerebral peduncle	0.19	0.37
Midbrain	1.05	1.31
Midbrain-tegmentum	2.79	4.20
Midbrain-tectum	0.51	0.74
Pons	7.95	11.26
Medulla	3.81	4.05

\* TBI = traumatic brain injury.

demonstrate even greater pathology that simply cannot be ascertained from the T1 image. For example, the T2 images provide better delineation of abnormal CSF collections, conspicuously involving almost the entirety of the frontal region at the level viewed, better appreciated than the dark signal seen in the T1 images. However, neither the T1 nor T2 images fully depict the extent of disseminated white matter abnormalities, as shown in the fluid attenuated inversion recovery images (FLAIR) or the residual hemorrhagic lesions as shown by the gradient recalled echo (GRE) images. Not shown here are other methods that detect abnormalities such as MR spectroscopy, magnetization transfer and white-matter coherence determined by diffusion tensor imaging (DTI, 1, 19, 20) that would likely demonstrate even additional abnormalities if applied to a case like that shown in Figure 15-7. Finally, when a functional imaging tool is used, such as single photon emission computed tomography (SPECT; see Figure 15-7), further clarity of the extent of functional impairment is evident by the widespread perfusion defects, even in some tissue where more normal signal is observed on MR imaging. Thus, what is defined as abnormal is dependent on imaging sequences and technology used, where each imaging method has its own set of limitations. Without taking into consideration all of these abnormalities in the predication of functional outcome, functional outcome predicted strictly from neuroimaging becomes problematic.

Lastly, an even more potentially insurmountable limitation of contemporary neuroimaging in predicting functional outcome is that even with our best existing neuroimaging tools, microstructure cannot be imaged. Inferences can be made about neurochemical composition of tissue via MR spectroscopy (MRS, 4,21) and diffusion tensor imaging permits identification of aggregate white matter tracts (see Figure 15-2 and Ref. 22) and their 'coherence' where optimal white matter shows lower apparent diffusion and higher fractional anisotropic coefficients (see 23), but actual microstructure can not be imaged in vivo at this time. That is not to say that tremendous strides are not occurring in exploring methods of neuroimaging of microanatomy (see 24), but the application of such structural imaging techniques is just now being applied to the study of functional recovery from TBI and its predication. Because of these limitations with structural imaging, it is likely that many of the advances in predicting TBI outcome will come from the integration of structural and functional neuroimaging (25, 26).

At the microstructure level, post-mortem cases have clearly shown widespread histopathological abnormalities, particularly in moderate to severe TBI (27-29), especially involving axonal damage (27, 30, 31) and disrupted neurotransmitter systems, but also mild TBI where gross abnormalities based on visual inspection are either absent or minimal (32-36). Since in structural neuroimaging the

threshold detection of abnormal signal using current MR technology is approximately a  $\text{mm}^3$ , whatever abnormality can be visualized in structural imaging represents the sum total of all underlying microstructure pathology. Returning to Figures 15-3 and 15-6, while the focal deficits are clearly evident, there is generalized damage. Presence of generalized damage suggests widespread microstructure pathology affecting the brain in a nonspecific fashion. This is not only readily depicted in the case shown in Figures 15-3 and 15-6 but can be shown by comparing the volumes of different brain structures from a TBI patient to a normative comparison as presented in Table 1, which was taken from the patient shown in Figure 15-7. Using quantitative methods, surface area measurements or actual volumes can be calculated from any brain region of interest (ROI) and compared to normative data, or an appropriately matched control (see Ref. 37). For the case presented in Figure 15-7 the patient's quantitative imaging findings are compared to an age and head size (i.e., intracranial volume) matched control subject. As can be seen, in all comparisons, including all of the subcortical structures, atrophy has occurred. As shown by the comparisons in Table 15-1, there is not a region that was spared 'injury', either directly or indirectly, in this case of severe TBI. This observation of widespread damage, both at the macroscopic (which neuroimaging can detect), as well as microscopic level in TBI, has led to the concept of diffuse brain injury (DBI), and will be described next. DBI may be the single most important factor that complicates predicting outcome from structural neuroimaging studies.

### NEUROIMAGING OF TRAUMATIC BRAIN INJURY (TBI) AS A DIFFUSE BRAIN INJURY (DBI)

Graham et al. (29) discuss TBI in the context of underlying general neuropathology, often referred to as DBI (see also Refs. 31, 38, 39). This is a very important concept to understand in interpreting functional outcome from structural imaging and, as will be shown by the discussion that follows, ventricular dilation in combination with reduced brain volume are indicators of DBI (37).

As introduced above, hydrocephalus ex vacuo is a commonplace occurrence in moderate-to-severe (i.e., Glasgow Coma Score, GCS < 12) TBI. This occurs because ventricular CSF is under pressure, which in turn creates an outward pressure gradient within the ventricle, which under normal conditions is kept in balance by brain mass and CSF reabsorption, so that a constant equilibrium is maintained between brain and ventricle. However, following TBI induced neuronal cell loss, brain parenchymal volume is reduced but ventricular CSF pressure (provided that some type of occlusive hydrocephalus is not present) remains constant. With the loss of parenchymal

volume there will be a natural, passive expansion of the ventricle. This is illustrated in all of the clinical cases presented so far (see Figures 15-3, 15-5, 15-6, and 15-7).

One of the most straightforward ways to quantify ventricular dilation or hydrocephalus ex vacuo in TBI patients is to compare the ratio of total ventricular volume to total brain volume, the so-called ventricle-to-brain ratio or VBR. Because the margins between the ventricular cavity and brain parenchyma are distinct on CT and/or MR imaging, VBR can be readily calculated using either imaging technology (Bigler, 1999). From mid-adolescence to late middle life, the VBR is relatively constant at about 1.5, with a standard deviation of approximately 0.5 (40, 41). This type of quantitative analysis can then be applied to scan findings at anytime post-injury in demonstrating trauma related DBI. For example, the case presented in Figure 15-8, demonstrates the use of VBR to show acute effects of cerebral edema (another potential generalized insult to the brain in TBI) and then ventricular expansion as an indicator of generalized parenchymal volume loss and DBI (42). This case is particularly helpful in demonstrating these points, as the patient had MR imaging done prior to injury, depicting normal ventricular size based on quantitative analyses. Increased levels of cerebral atrophy, as measured by VBR or other indices of parenchymal volume loss, relate negatively to overall outcome (43).

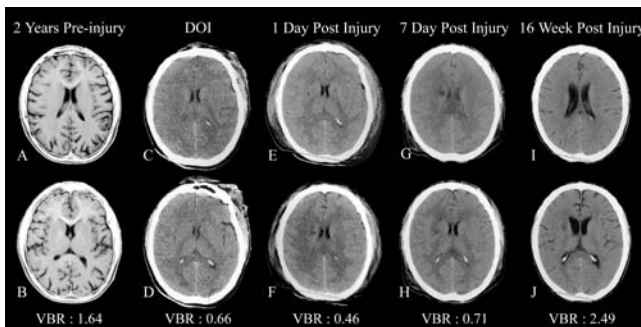


FIGURE 15-8

Axial MR (A, B) taken prior to injury, compared to follow-up computerized tomography (CT, images C-F) imaging done on the day-of-injury (DOI, shown in C and D) and at different times post-injury. Note the compression of the ventricular system (smaller size) on the DOI scan, representative of generalized cerebral edema. The patient's pre-traumatic brain injury (TBI) ventricle-to-brain ratio (VBR), shown at the bottom, was well within normal limits (normal VBR ~1.5, standard deviation = 0.5), but on the DOI scan and the acute stage post-injury, VBR is significantly reduced, again another indicator of generalized cerebral edema. By four months post-injury (I, J) significant ventricular dilation has occurred and VBR has risen to approximately two standard deviations above the mean, reflective of generalized brain volume loss secondary to trauma induced generalized degeneration. This patient had a Marshall et al., (65) level III (swelling) clinical rating of the DOI CT scan (see Table 15-2)

VBR is related to all severity of injury measures in a rather linear fashion, as shown in Figure 15-9, including GCS, loss of consciousness (LOC) and post trauma amnesia (PTA) (44) and any adverse systemic effects such as hypoxia (42). Unmistakably, ventricular dilation of the nature observed in TBI results from DBI and is likely the best single measure of DBI. Based on this assumption, larger VBR reflects generalized atrophy and therefore represents a severity marker of neuropathological changes. Larger VBR is associated with worse cognitive outcome and greater neurobehavioral sequela of acquired brain injury (37).

Unfortunately, quantitative analyses are often not available to the clinician, so how does one best evaluate ventricular dilation and cerebral atrophy, short of quantitative analyses? Actually, this can be readily performed with a straightforward visual inspection of either CT or MR findings, since small ventricular size is the norm in the noninjured brain until after the sixth decade of life (41). Since this is more completely addressed in a following section, only brief mention will be made here. Even when substantial acute pathological changes are present in the initial CT scan done on hospital admission following TBI, the DOI scan provides baseline information

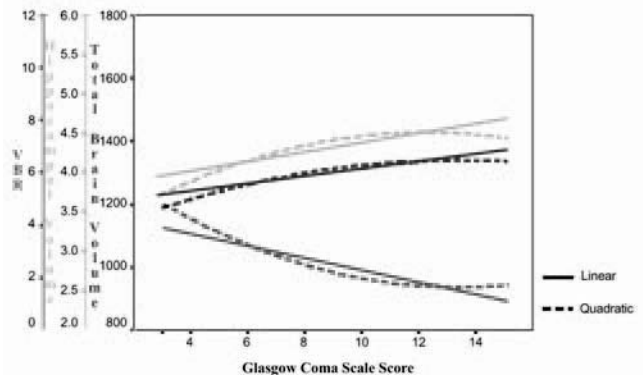


FIGURE 15-9

This illustration is from our ongoing traumatic brain injury (TBI) data base and represents 151 subjects with varying levels of severity of injury as defined by Glasgow Coma Scale (GCS). Plotting either brain volume, hippocampal volume, or the ventricle-to-brain ratio (VBR, a measure of global atrophy) results in linear and quadratic relationships that demonstrate brain or hippocampal atrophy is directly related to the severity of injury. Note that the relationship is best fit by a linear rather than quadratic function for whole brain volume (Blue color), the ventricle-to-brain ratio (Red color) or hippocampal volume (Yellow color). The hippocampal data is based on a subset comprised of 46 subjects. In each case there is a linear loss of brain parenchymal volume directly related to severity of injury. Accordingly, loss of tissue is a function of severity of injury. Similar plots are achieved if PTA or LOC are substituted for GCS. Adapted from Bigler et al. (119)



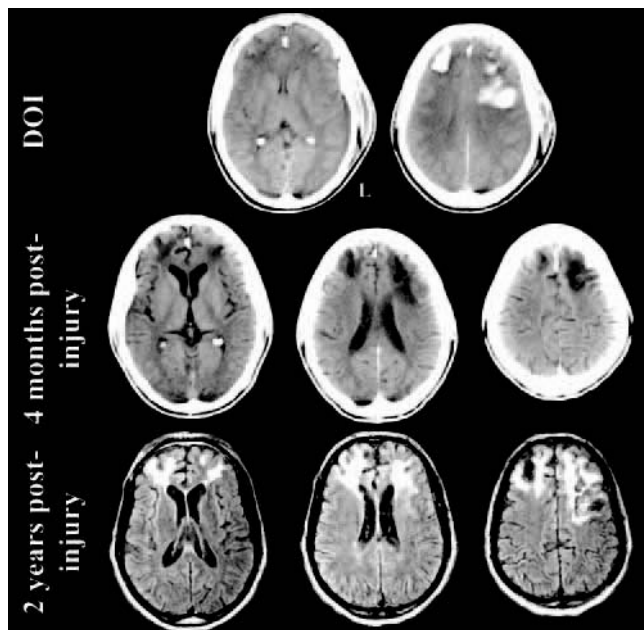


FIGURE 15-10

Day-of-injury (DOI) axial computerized tomography (CT) scans demonstrated multiple frontal hemorrhagic contusions and intraparenchymal areas of hemorrhage and edema, with compression of the anterior horns of the lateral ventricle. By four months post injury, follow-up CT demonstrates loss of density in frontal tissue, with corresponding dilation of the anterior horns of the lateral ventricle. However, the entire ventricular system is also showing expansion (hydrocephalus ex vacuo), reflective of generalized degeneration. By two years post-injury, fluid attenuated inversion recovery images (FLAIR) magnetic resonance (MR) imaging demonstrates generalized ventricular enlargement and extensive signal abnormality widely distributed across the frontal regions, bilaterally. This illustration demonstrates the utility of comparing DOI imaging to subsequent imaging studies and how this permits easy tracking of degenerative changes (i.e., ventricular dilation)

about preinjury ventricular size. As shown in Figure 15-10, this patient sustained a severe head injury as a consequence of an auto-pedestrian accident, and DOI CT findings demonstrated extensive frontal hemorrhagic lesions. Nonetheless, ventricular size can still be distinguished, even though generalized edema had developed by the time that the initial CT scan was obtained. On the DOI scan, small anterior horns of the lateral ventricular system can be readily identified, although somewhat effaced by the surrounding edema. In comparison, by the chronic stage, all follow up scans demonstrated ventricular dilation as well as changes in frontal parenchyma. Thus, clinicians should not only view the DOI imaging to identify acute pathology, but also as a benchmark for what the brain looked like before injury. Another way to view trauma induced atrophy, or DBI, is by viewing the midsagittal plane, where not

only the body of the lateral ventricle can be observed, but the corpus callosum (CC) as exemplified in Figure 15-6. Figure 15-6 compares the midsagittal MR view and a 3-D comparison of the ventricular system in the case presented in Figure 15-3 to show the diffuse nature of moderate to severe TBI as expressed by ventricular dilation and CC atrophy. Regardless of how it is demonstrated (i.e., simple visual inspection and interpretation, quantitative measures such as increased VBR, increased clinical atrophy ratings [see below] or thinning of the CC, etc.), presence of generalized cerebral atrophy is a predictor of cognitive, neuropsychiatric and neurobehavioral sequelae (2, 5, 6, 37, 45, 46).

What has just been discussed brings up another issue that demonstrates the complexities and challenges of establishing brain-behavior relationships in predicting functional outcome in TBI. For those who survive significant brain injury and ‘recover’ whatever function or make whatever type of adaptation possible, structural imaging will mainly highlight the lesion or damage, which is probably not where functional reorganization is or has taken place (26, 47–49). For example, in the case presented in Figure 15-5 where extensive cortical wasting, particularly of the left frontal region, had occurred, frontal damage originally resulted in a generalized expressive aphasia that lasted several months. However, after an extended recovery and rehabilitation period, this patient eventually recovered verbal abilities to the point of obtaining a verbal IQ score of 100 and a normal score on confrontational naming, performances that reflect general intactness of language. He still had some diminished word fluency, but the more significant changes were in personality, drive and temperament, not language. Obviously, the abnormalities that reflect absence of and/or nonfunctional tissue do not necessarily represent the regions of the brain that have adapted. Research in this area has shown that functional reorganization occurs in regions that have been spared or less damaged, often distributed in a fashion that cannot be fully predicted due to individual differences, and often in regions not traditionally associated with such functions (50, 51).

This issue of functional adaptation has been nicely demonstrated by Mathias et al. (52) who has studied reaction time and speed of processing in mild to severe TBI. If white matter is particularly vulnerable to brain injury, structurally identified by reduced CC surface area, this would suggest disrupted interhemispheric white matter projection and interhemispheric transfer of information. However, Mathias et al. (52) as well as others (53–55) have shown that the degree of CC atrophy only modestly, and in many cases nonsignificantly, relates to deficits in interhemispheric transfer observed in patients with TBI. In other words, the CC is critical for transfer and integration of information between the two hemispheres and is clearly vulnerable in TBI (see Figure 15-6), but despite presence of CC lesions and atrophic changes, for the most part TBI patients

recover the ability to carry on interhemispheric transfer of information and reaction time tasks, albeit slower than their non-TBI matched cohorts. Rarely do TBI patients have a lasting callosal syndrome (56). So, even though significant CC atrophy occurs in brain injury and is related to severity of injury, somehow the injured brain adapts and interhemispheric transfer of information occurs. When such adaptation occurs, using just structural neuroimaging as the basis for measuring the atrophy of the CC results in minimal power to predict impairment. The point here is that when some functional recovery has taken place, structural imaging of damaged tissue may not capture how the brain has adapted, it only measures the original region(s) of damage. Chapter 16 on functional imaging will have more to say about this problem, and the future of predicting functional outcome will probably come from the integration of structural and functional imaging.

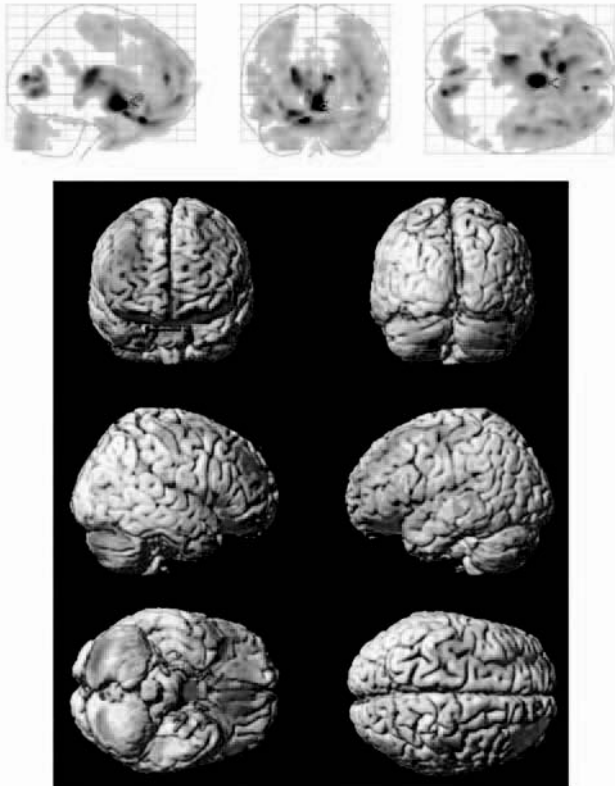


FIGURE 15-11

Statistical parametric mapping (SPM, top black and white plots) of a voxel-by-voxel quantification of damage (shown in red in the 3-D brain representations) from a group of TBI subjects who had sustained frontal or temporal lobe contusions. VBM analyses where red represents decreased gray matter density in six TBI adolescents (mean age = 16 years old, standard deviation = 5.1) all with moderate-to-severe TBI (all had had GCS scores of 8 or below) compared to 18 control subjects of similar age (three control subjects per TBI patient within 2 years of age). Note the predominance of frontotemporal damage

In summary thus far, the mere presence of imaging abnormalities from trauma are not sufficient, by today's understanding of brain-behavior relationships to fully predict functional outcome. What may appear straight-forward (i.e., simply comparing 'lesions' to outcome) actually represents a very complex clinical question. Restrictions of current neuroimaging methods to fully integrate all levels and types of abnormalities from cerebral trauma into a prediction model, means that any one identified neuroimaging abnormality, by itself, often lacks robust relationship with functional outcome (57, 58). The exception here, as will be discussed later, is with brainstem abnormalities.

### Vulnerability of Frontal and Temporal Regions

The earliest post-mortem TBI studies demonstrating the most likely regions of contusion confirmed the predilection for frontal and temporal locations (59). More contemporary neuroimaging studies have clearly demonstrated the greater likelihood of frontal-temporal damage over damage to any other brain region in cases of TBI (60) and can be shown when voxel-based morphometry (VBM) is used to compare those with brain injury versus control subjects as presented in Figure 15-11. A dorsal view of a skull, with the skull cap removed, is shown in Figure 15-12, clearly demonstrating the location of the

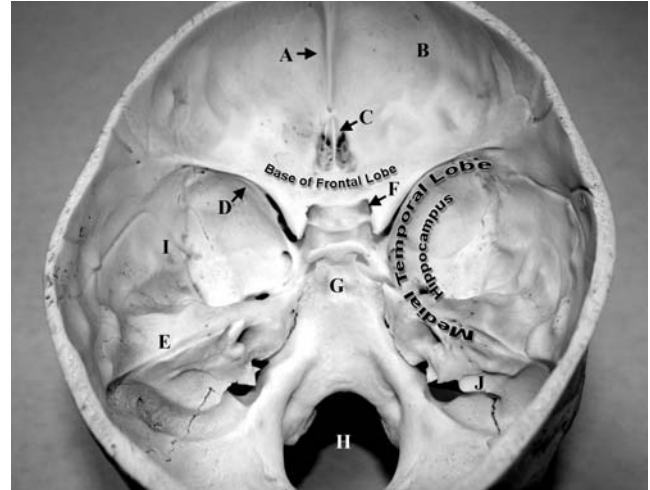


FIGURE 15-12

Dorsal view of the open human skull (skull cap removed), where the skull cap has been removed. Top of the picture is just above the orbit. The general location of the base of the frontal lobe (jugum of the sphenoid bone) and location of the medial temporal lobe is outlined in bold letters. A: Frontal crest, B: Orbital part of frontal bone and anterior cranial fossa, C: Crista galli, D: Sphenoid, E: Petrous part of temporal bone, F: Anterior clinoid process, arrow points into the pituitary fossa or sella turcica, G: dorsum sellae above with clivus extending down, H: Foramen magnum, I: Middle cranial fossa, J: Posterior cranial fossa

anterior, middle and posterior cranial fossa. The ventral surface of the frontal lobe is situated in the anterior cranial fossa, the ventral surface of the temporal lobe in the middle cranial fossa and the cerebellum in the posterior cranial fossa. For slight movement and minimal impact, the three cranial fossa create protective factors to hold the brain in place. However, the soft, pliable brain is no match against the hard inner table of the skull once inertial forces exceed its tolerance limits. Mechanical deformation of the brain against bone, not only injures the parenchyma through mechanisms of compression and stretching (31), but increases the likelihood of contusion (61, 62). Using the integration of CT, that permits detailed identification of the bones of the skull, and MRI, that permits detailed identification of brain structures, the vulnerability of these regions is easy to appreciate because of how they are partially cradled and encapsulated by bone as shown in Figure 15-13. Thus, the undersurface of both the frontal and temporal regions become particularly vulnerable to mechanical deformation and/or contusion against bony structures as well as the anterior aspect of the temporal lobe against the sphenoid bone and the medial aspect of the temporal lobe against the sphenoid and petrous bones and clinoid process. Likewise, the basal forebrain sits just anterior to the clinoid process and the jugum of the sphenoid, both regions that have some potential for protrusion into the base of the frontal lobe. Likewise, more anteriorly, the frontal bone plate just above the nasal-orbital region, as shown in Figure 15-12, has several prominent ridges. Understanding this part of the

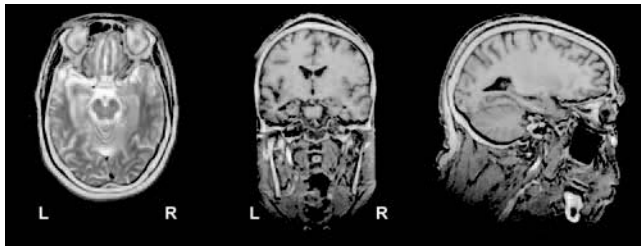


FIGURE 15-13

From left to right, fused spiral CT bone window imaging of the skull (shown in pink) interfaced with MRI in axial (T2), coronal (T1) and sagittal (T1). Bone is shown in pink to highlight how the brain is encapsulated by the cranium, particularly the anterior and middle cranial fossa. This patient sustained a moderate TBI with left temporal petrous bone fracture, that had healed by the time imaging was obtained. However, not the increased CSF in the anterior pole in the T2 Axial view shown on the left. Likewise, the coronal view in the middle demonstrates temporal lobe atrophy (temporal horn dilation, reduced size of hippocampus compared to the contralateral size of the hippocampus), reduced temporal stem. Quantitative analyses demonstrated overall reduced temporal lobe white matter volume, reduced since of entorhinal cortex, hippocampal and amygdala volumes

brain-skull interface becomes particularly important in understanding the behavioral significance of neuroimaging findings in TBI and the increased likelihood of inferior frontal and anteromedial temporal lobe damage (see 62), as clearly demonstrated by the VBM analysis shown in Figure 15-11.

Given that there is greater frontotemporal lobe damage associated with TBI, it is no surprise that the most common neuropsychological sequelae associated with TBI are those in the realm of memory and executive impairment (60). Since memory, particularly working memory, is central to all aspects of executive function, it may be that the single most important cognitive function typically disrupted by TBI is some aspect of memory (61, 63). Budson and Price (64) have recently reviewed the gross neuroanatomy associated with memory dysfunction as depicted in Figure 15-14. By comparing the illustration of the brain regions typically damaged in TBI, as shown by the VBM analysis presented in Figure 15-11, it should come as no surprise why some impairment in memory is such a common feature in TBI. Budson and Price (64) go on to provide more details as to key structures involved in various types of memory and that is presented in Figure 15-14. As can be seen major frontotemporolimbic regions and pathways are at the basis of the key structures that underlie memory function. What is of particular interest in linking TBI to neuroimaging findings and cognitive outcome, is that each structure depicted in Figure 15-14 has been shown to be affected by TBI and in the case presented in Table 15-1 and Figure 15-7, each of the areas key to memory function were damaged. Accordingly, Figure 15-14 can be used as a guide to the type of memory dysfunction that may result from a brain injury, depending of the location and extent of involvement of a particular brain region.

### NEUROIMAGING OF ACUTE INJURY AND PREDICTION OF OUTCOME

Although from the above discussion, it is easy to see why the effects of TBI are more complicated than just location of a lesion(s) that predicts neurobehavioral outcome, it is still important to understand how lesions begin and evolve following trauma, and how the earliest lesions identified by neuroimaging relate to functional outcome. Using acute imaging compared to sub-acute and chronic imaging and tracking lesions and atrophic changes may yield far more important predictive statements about outcome, than just a single static image, usually during the chronic stage, to predict functional outcome. Since the first neuroimaging study of someone with a brain injury is typically a CT scan on the day-of-injury (DOI), this Chapter will next overview the relationship between the DOI CT scan and functional outcome. The DOI scan serves another purpose as well (as introduced above) that

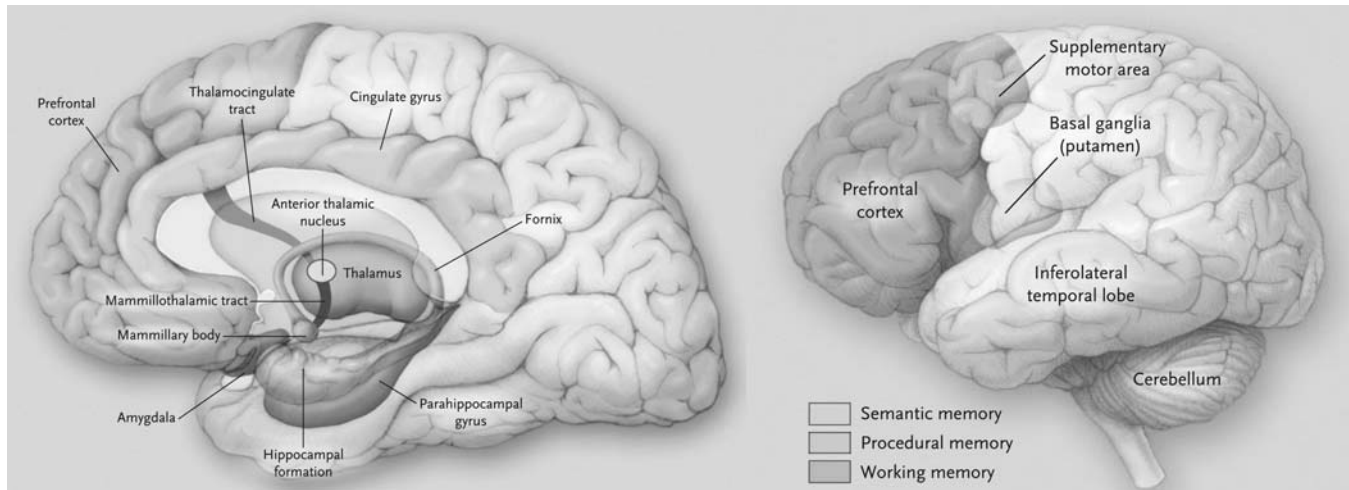


FIGURE 15-14

*Left:* The medial temporal lobes, including the hippocampus and parahippocampus, form the core of the episodic memory system. Other brain regions are also necessary for episodic memory to function correctly. *Right:* The inferolateral temporal lobes are important in the naming and categorization tasks by which semantic memory is typically assessed. However, in the broadest sense, semantic memory may reside in multiple and diverse cortical areas that are related to various types of knowledge. The basal ganglia, cerebellum, and supplementary motor area are critical for procedural memory. The prefrontal cortex is active in virtually all working memory tasks. Other cortical and subcortical brain regions will also be active, depending on the type and complexity of the working memory task. Used with permission of Budson and Price (64) and NEJM

of establishing a baseline to track changes overtime. Thus, comparing follow-up CT or MR imaging to the DOI scan (as in Figures 15-8 and 15-10) often provides more useful information relating to predication of outcome from brain injury; such comparisons will be the basis of the concluding topic.

Much of the interpretation of DOI CT scans has already been addressed in chapter 11 and therefore this section will concentrate not so much on lesion identification, but on the relationship between these lesions and functional outcome. Figure 15-15 summarizes the typical lesions seen on acute CT imaging in cases of cerebral trauma where CT imaging is positive. These types of abnormalities, as well as other common trauma related abnormalities, can be simply classified and rated, as shown in Table 15-2 based on the work of Marshall et al. (65). This guide can be used to establish severity of abnormalities as found in acute imaging, as will be discussed and elaborated upon in the next section, where acute imaging findings are used to predict functional outcome.

#### DAY-OF-INJURY (DOI) COMPUTERIZED TOMOGRAPHY (CT) AND PREDICTION OF OUTCOME

The scale established by Marshall et al. (65) attempted to characterize trauma induced acute abnormalities on a nominal rating scale grading computerized tomography (CT) abnormalities from not discernible (Grade I) to

diffuse (Grade IV), as well as whether a hematoma was present (Grade VI), or had to be evacuated (Grade V), along with presence of brainstem pathology (Grade VII). These classifications by Marshall et al. are more completely detailed in Table 15-2 and the different type of acute traumatic lesions seen on CT as presented in Figure 15-15, in turn result in distinct likelihood of frontotemporal atrophy as already shown in most of the previous examples given in this chapter, and specifically shown in Figure 15-16. The patient shown in Figure 15-16 sustained a moderate-to-severe TBI in an auto-pedestrian accident with bilateral temporal contusions and development of a subdural, which was evacuated. The neuroimaging done more than two years post injury demonstrates the frontotemporal locus of damage. This patient's initial DOI CT scan would have been rated a III by the standards outlined in Table 15-2.

In a comprehensive study that examined 240 consecutive admissions at a Trauma I hospital for head injury who survived sufficiently to progress to an inpatient rehabilitation unit, we were able to examine the predictability of CT findings based on the Marshall et al. (65) rating system to outcome at various stages during the recovery process (see Refs. 9, 66). For these 240 subjects the mean GCS was approximately 9, with an average of several days of unconsciousness and an average PTA of 2 to 3 weeks. Accordingly, as a group, these subjects generally sustained moderate-to-severe TBI and represented the typical course of outcome following inpatient rehabilitation. Using the Marshall et al. (65) classification method, the most common lesions present on the DOI CT scan were Level

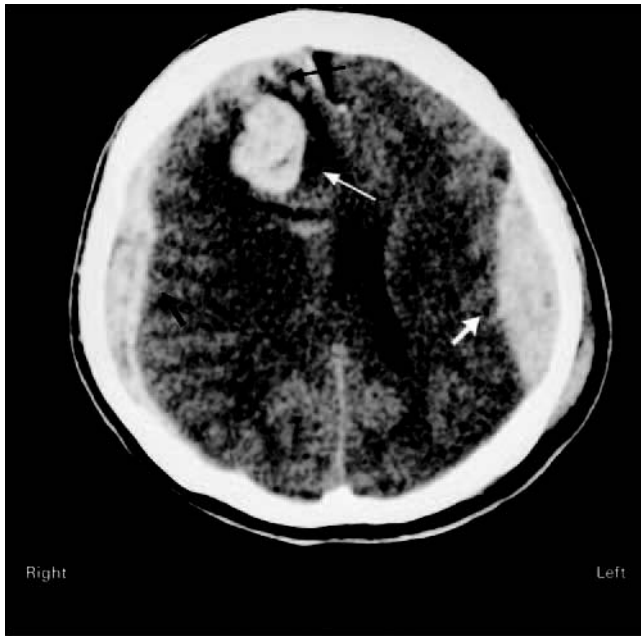


FIGURE 15-15

The axial section of a computerized tomography (CT) scan of the head at the level of the lateral ventricles, obtained without the addition of contrast medium, revealed four types of acute post-traumatic intracranial hemorrhage (Left is on the reader's right side); an epidural hematoma (thick white arrow) and a squamous temporal fracture (which is not shown) on the left side, a laminar subdural hematoma (thick black arrow) on the right side, right-sided periventricular and frontal-lobar contusions containing an intraparenchymal hematoma (thin white arrow), and a subarachnoid hemorrhage (thin black arrow) in the right frontal region. These injuries were sustained in a fall. (Reproduced with permission from Mattiello & Munz, (120) and the *New England Journal of Medicine*. Copyright © Massachusetts Medical Society.) Had this patient received a Marshall et al. (52) rating, it would be a level IV (see Table 15-2)

II (some diffuse swelling and presence of some petechial hemorrhages or small contusions). In fact amongst these 240 hospitalized subjects, almost 60 percent of all CT scans were so classified, whereas about 13 percent had Level I findings, 17 percent had Level III findings, approximately 4 percent with Level IV and 3 percent with Level VII. About 17 percent had some type of mass lesion. Since this study was based on the initial or DOI CT scan, no one had a mass lesion removed at that point, therefore no Level V subjects were part of this study. Despite clear-cut findings of pathology on the DOI CT scan (i.e., > Level II),

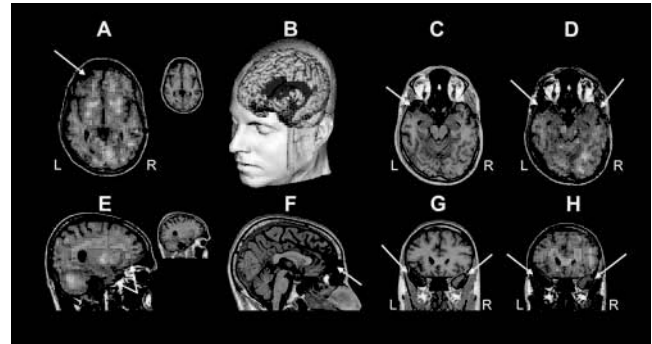


FIGURE 15-16

This illustration demonstrates the vulnerability of frontal and temporal regions for focal brain injury following traumatic brain injury (TBI). The 3-D reconstruction shown in B, highlights the frontotemporal damage in red as identified in multiple planes of magnetic resonance (MR) and fused MR-single photon emission computed tomography (SPECT) imaging, where arrows point to regions of focal encephalomalacia. D is the fused SPECT image with the axial MR shown in C and H represents the coronal fused MR-SPECT, where distinct focal temporal lobe encephalomalacia is evident in G. L designates left, R designates R. For A and E, the inset shows the level for the fused MR-SPECT image

TABLE 15-2<sup>≠</sup>  
Descriptive Categories of Abnormalities Visualized on CT\* Scanning

LEVEL	DEFINITION
I	Diffuse Injury I (no visible pathology)
II	Diffuse Injury II
III	Diffuse Injury III (swelling)
IV	Diffuse Injury IV (shift)
V	Evacuated mass lesion
VI	Non-evacuated mass lesion
VII	Brain stem injury

No visible intracranial pathology seen on CT scan  
 Cisterns are present with midline shift 0-5 mm and /or: lesion densities present; no high- or mixed-density lesion >25cc; may include bone fragments and foreign bodies  
 Cisterns compressed or absent with midline shifts 0-5 mm; no high- or mixed-density lesion >25cc  
 Midline shift >5mm, no high- or mixed-density lesion >25cc  
 Any lesion surgically evacuated  
 High- or mixed-density lesion >25cc, not surgically evacuated  
 Focal brainstem lesion, no other lesion presenty

<sup>≠</sup> Based on Ref. 65.  
 \*CT = computerized tomography.

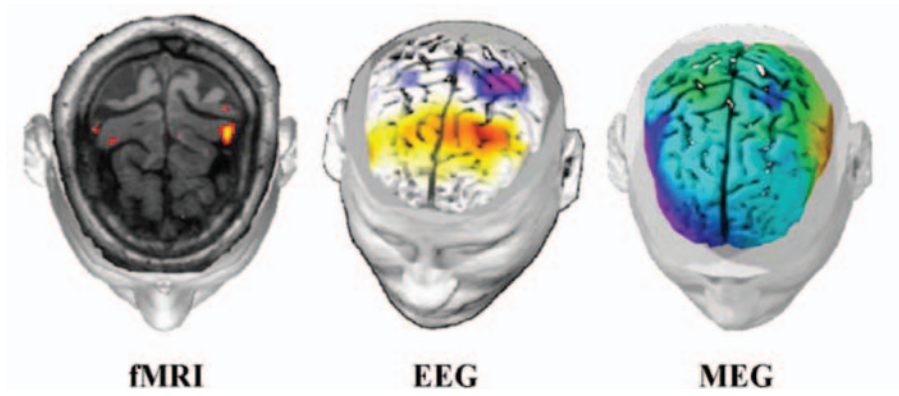


FIGURE 15-1

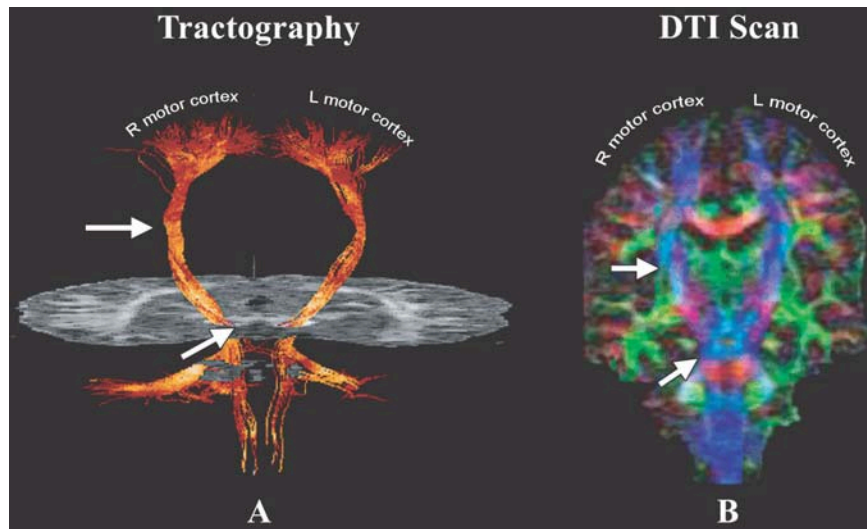


FIGURE 15-2

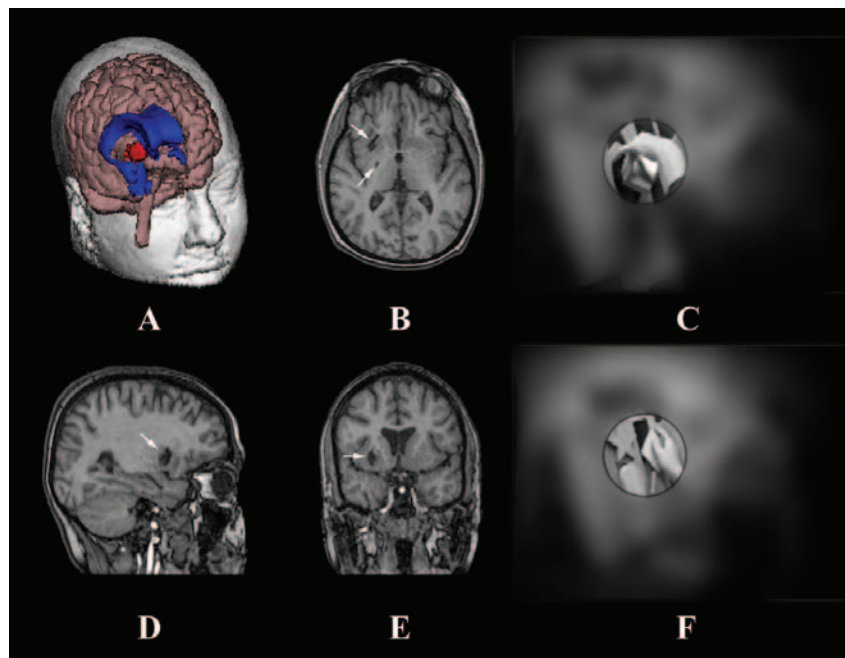


FIGURE 15-3



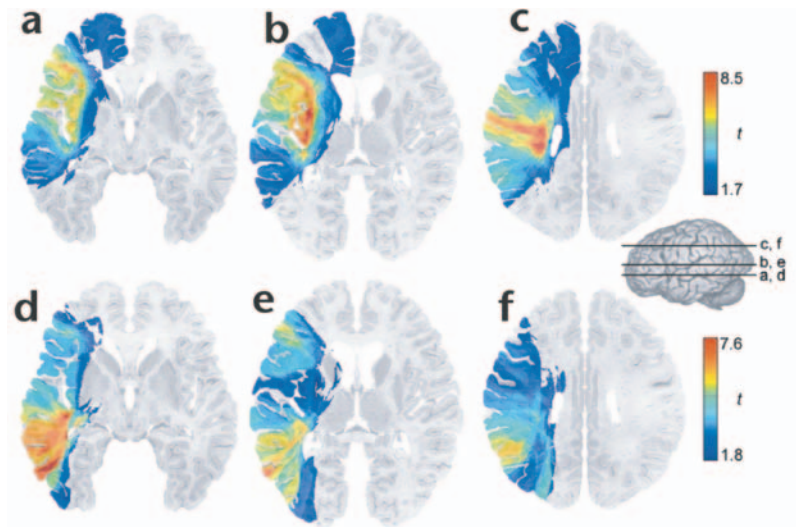


FIGURE 15-4

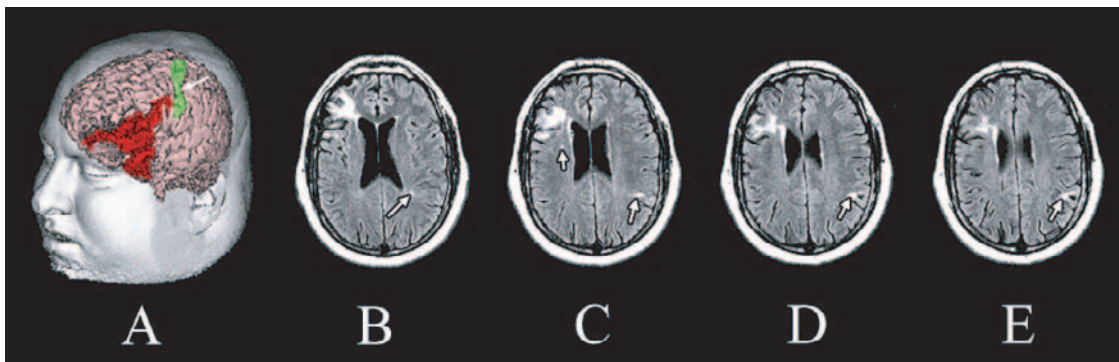


FIGURE 15-5

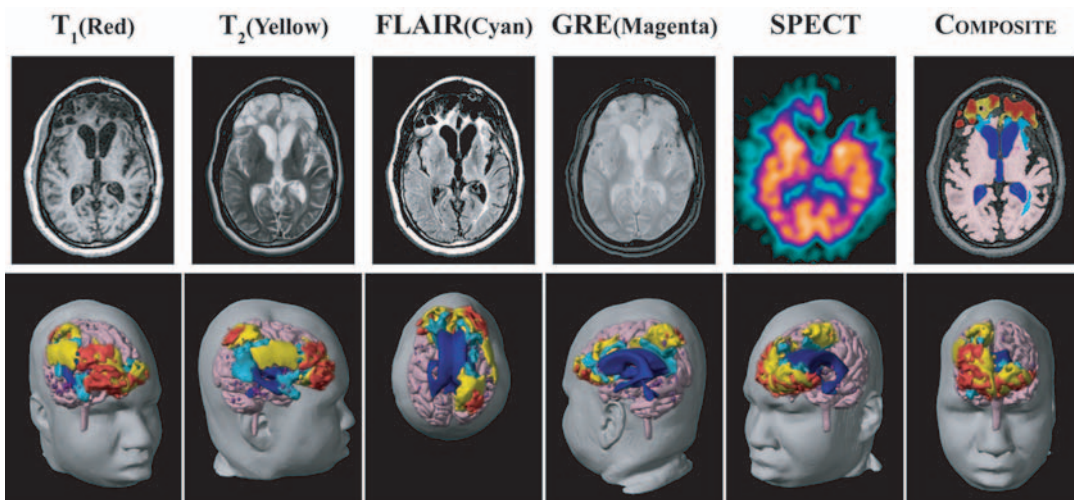


FIGURE 15-7

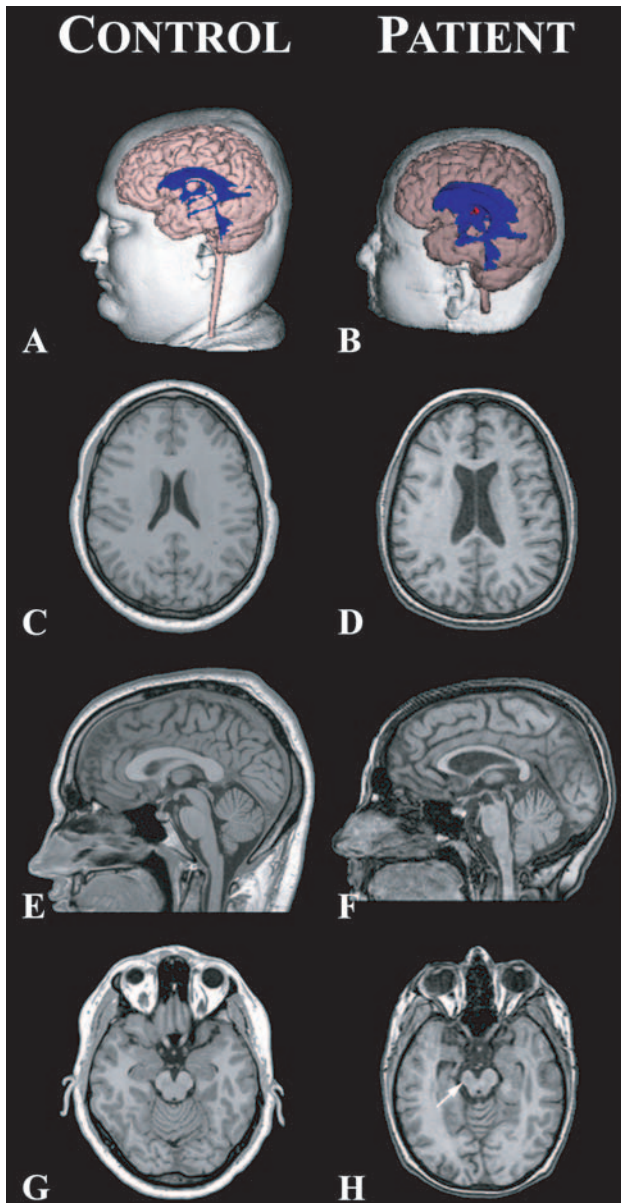


FIGURE 15-6

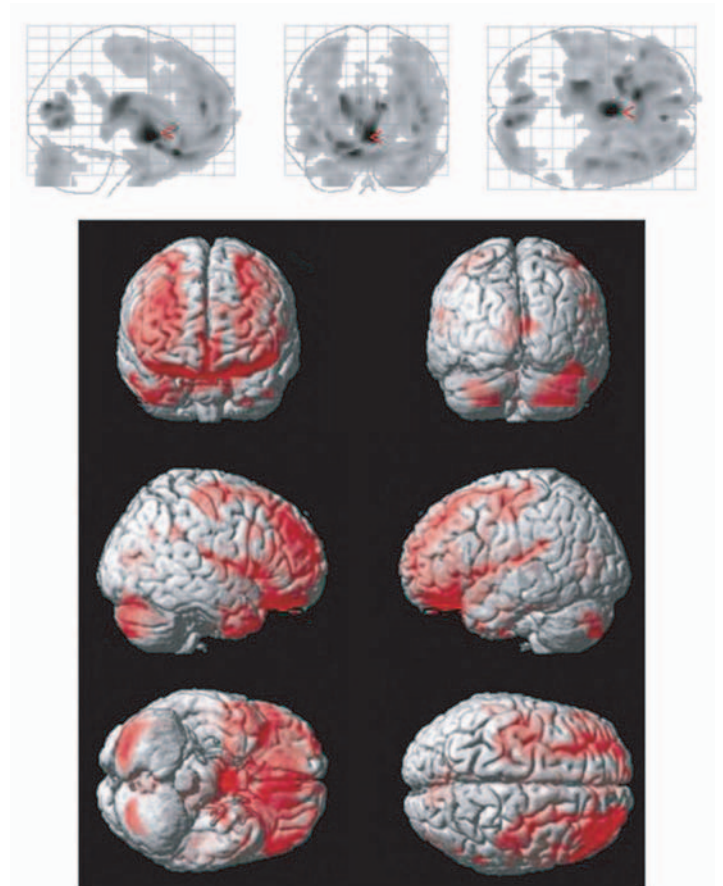


FIGURE 15-11

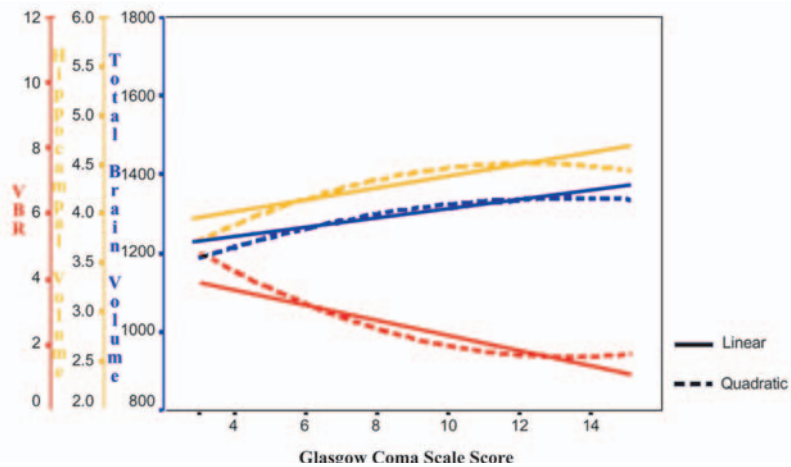


FIGURE 15-9



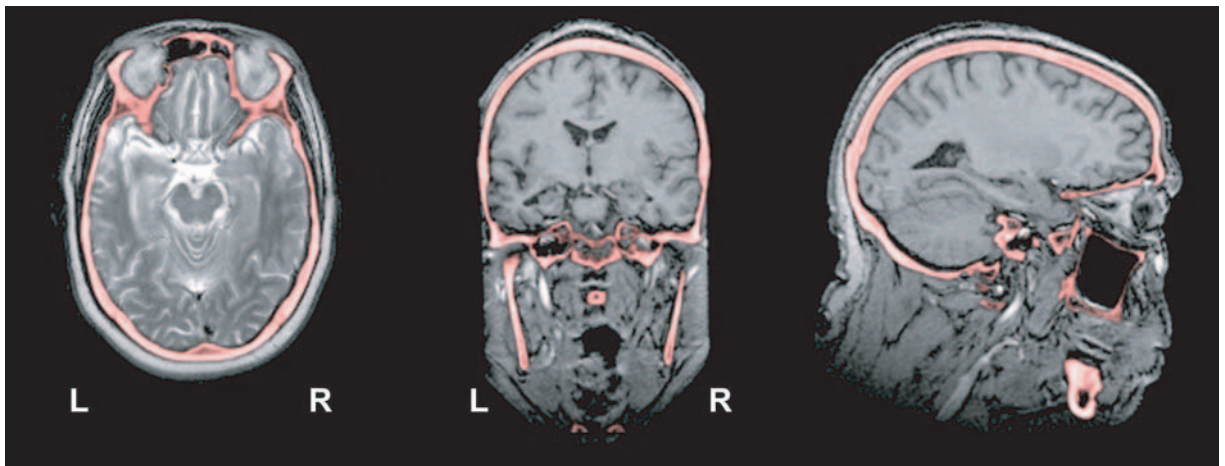


FIGURE 15-13

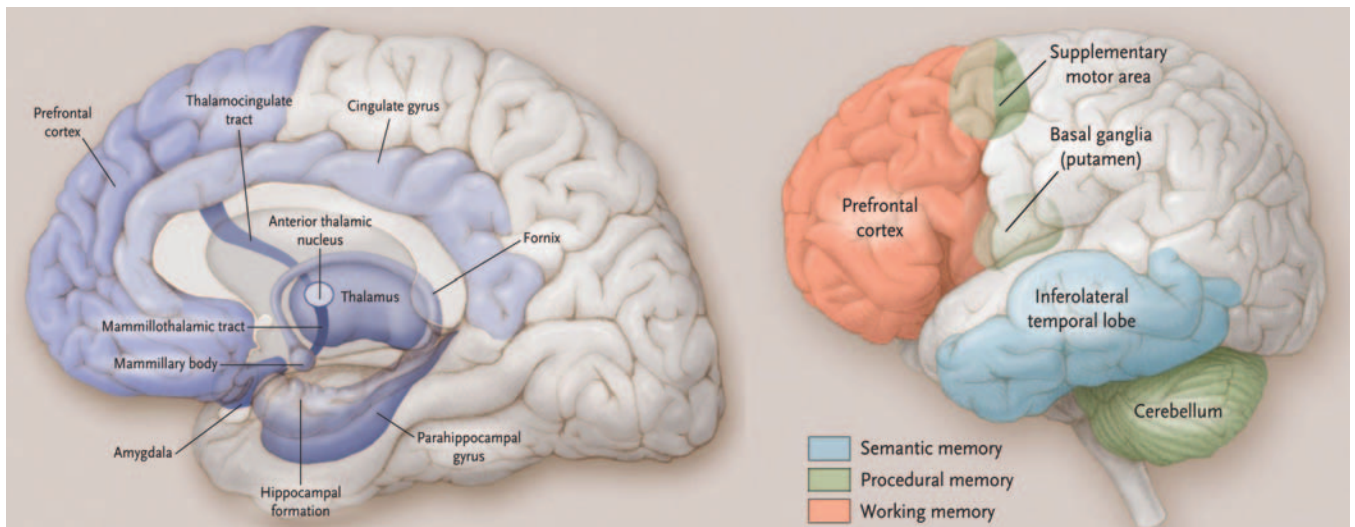


FIGURE 15-14

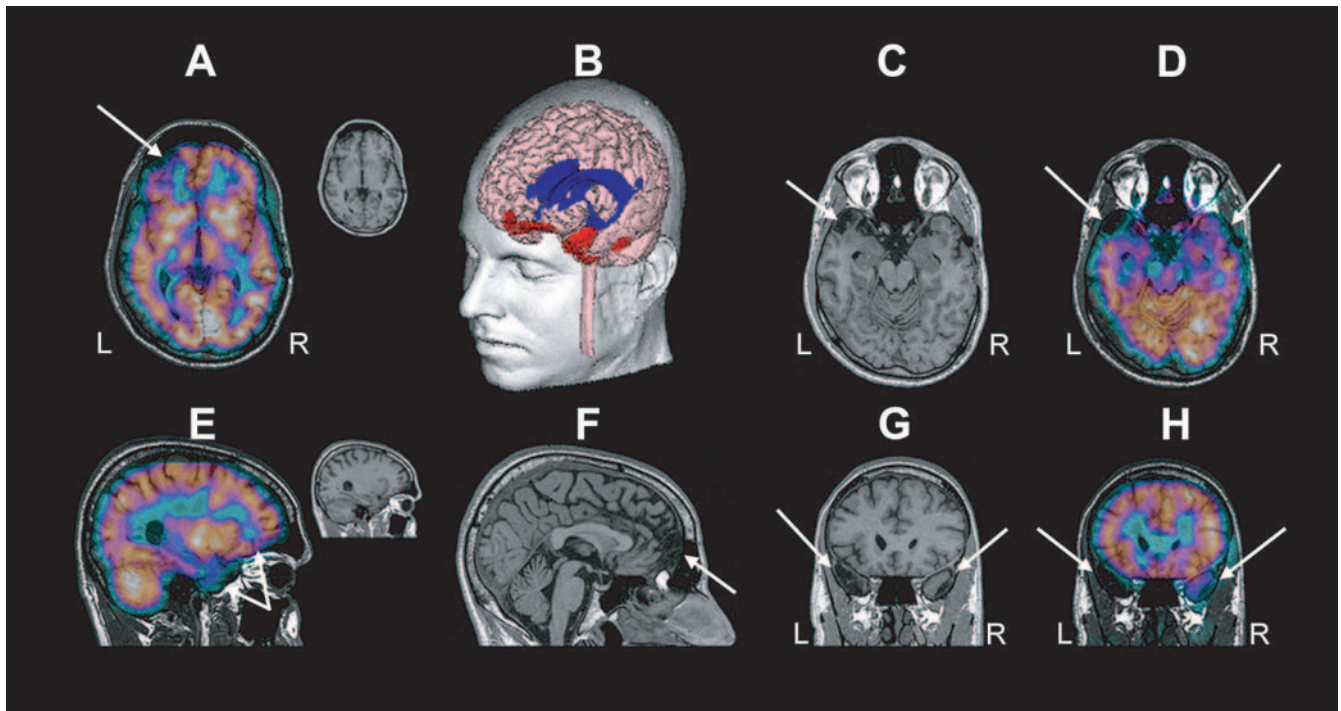


FIGURE 15-16

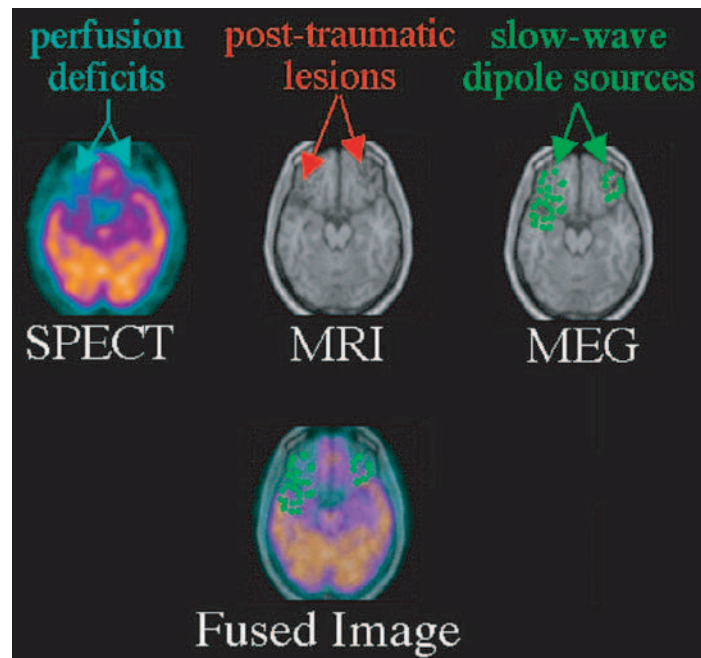


FIGURE 15-28

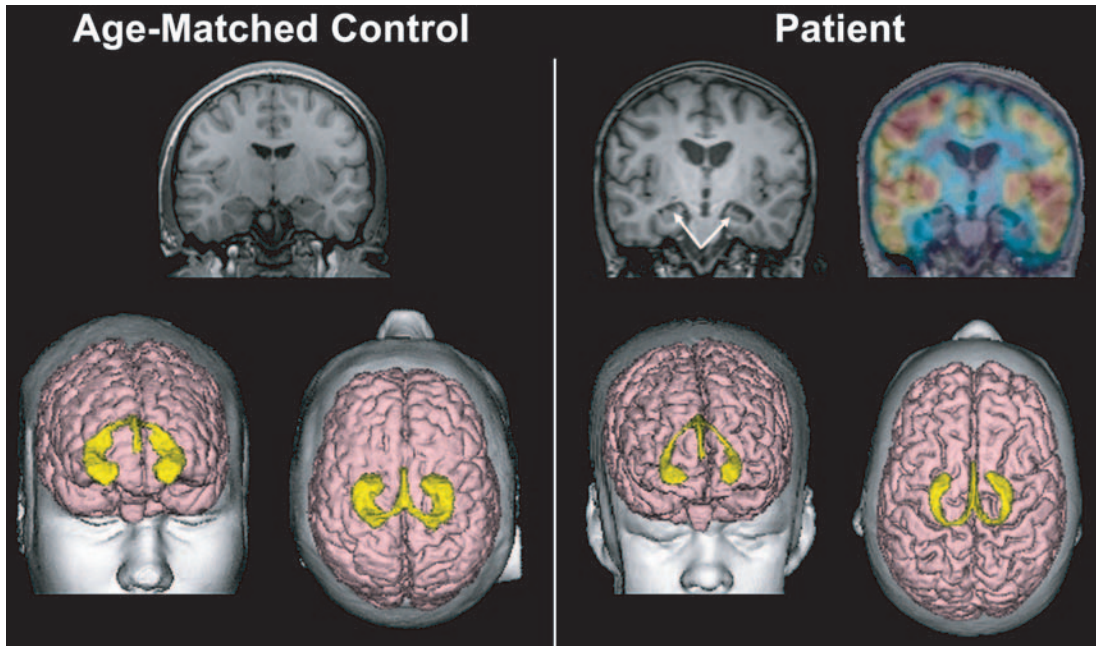


FIGURE 15-29

Minimally Conscious  
State Patient

Normal Subject

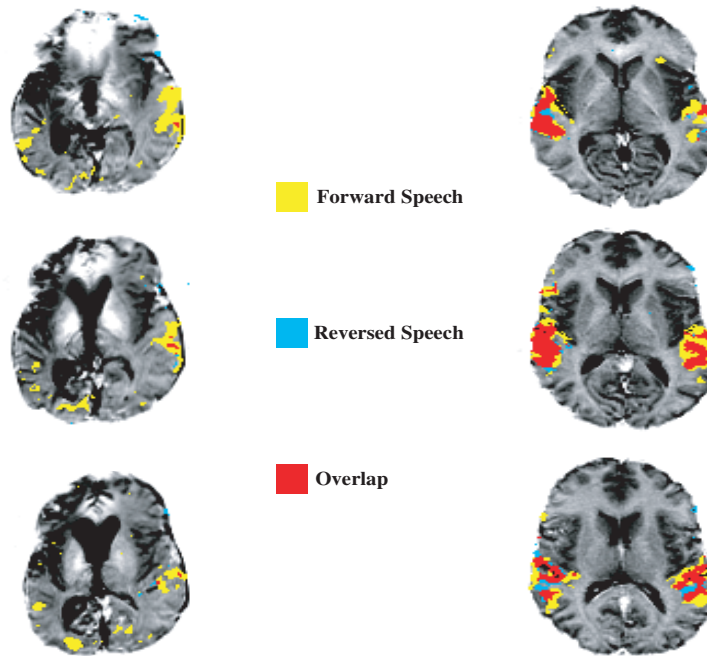


FIGURE 25-1



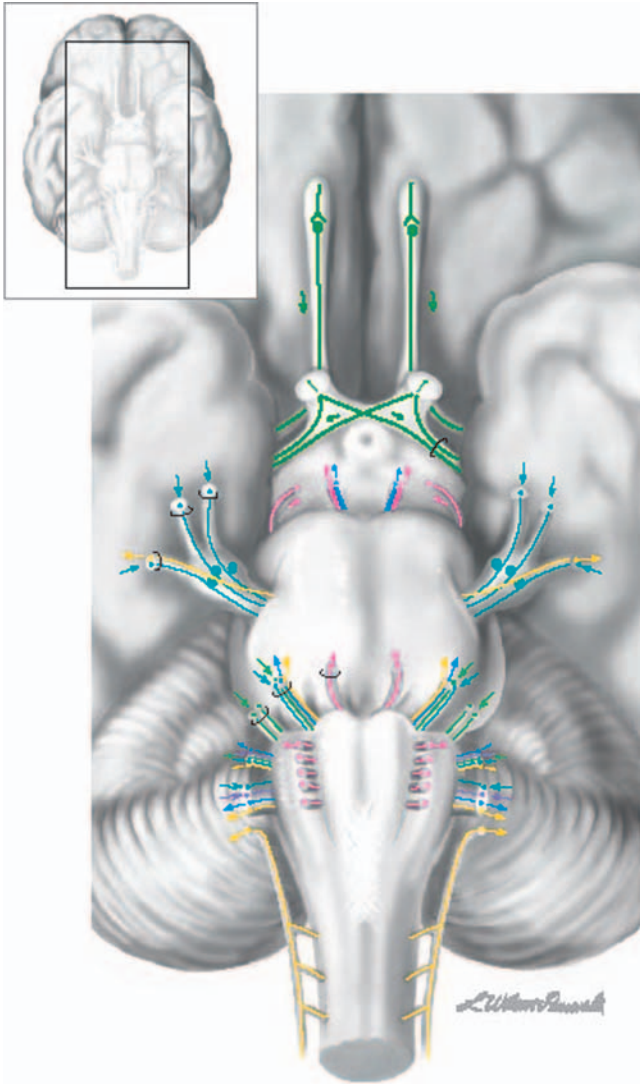


FIGURE 30-1

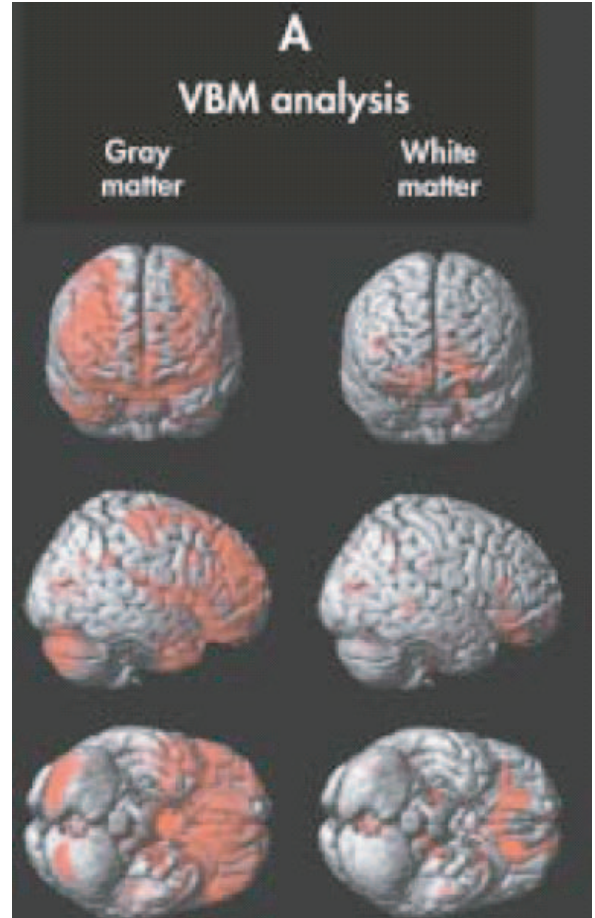


FIGURE 45-1

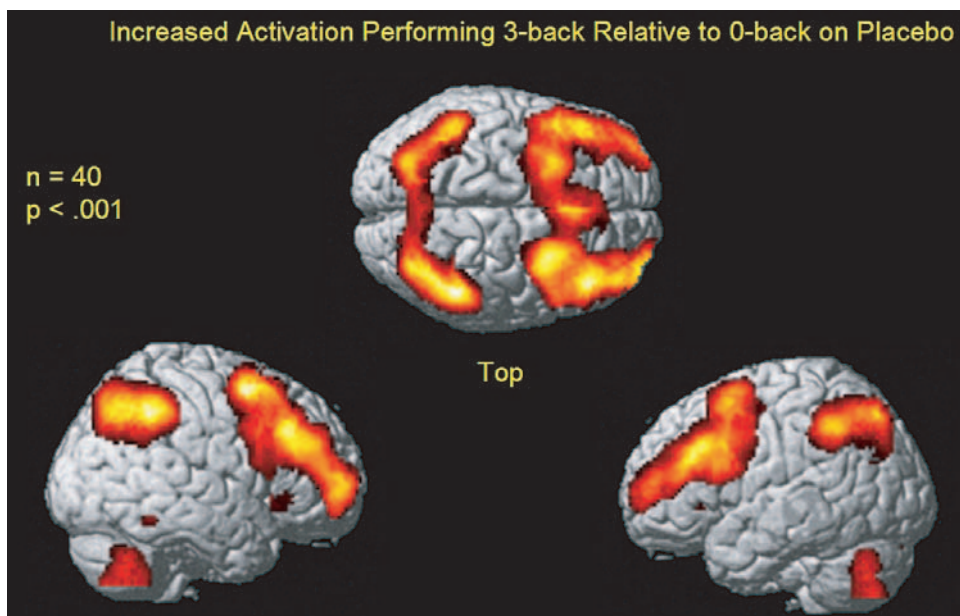


FIGURE 45-3

## Regional Cortical Vulnerability to TBI Predicts Neuropsychiatric Sequelae

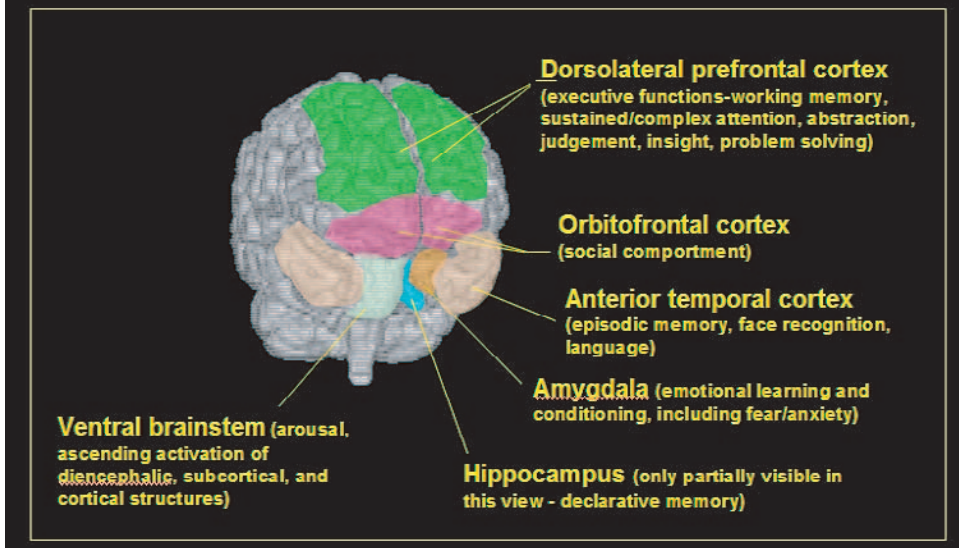


FIGURE 45-5

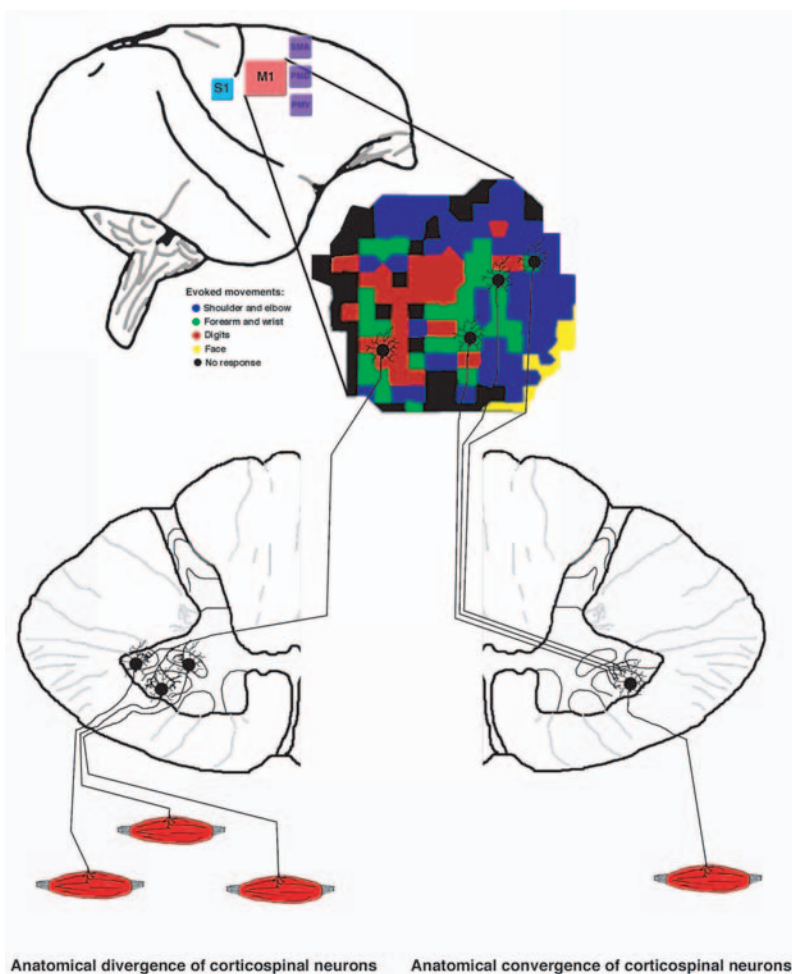


FIGURE 49-3

such findings were not very predictive of outcome at the time of admission to rehabilitation, rehabilitation discharge, or one year followup using the Functional Independence Measure (67, 68) or the Disability Rating Scale (DRS, 69), except for those with abnormal brainstem findings on CT. Presence of a brainstem lesion was a negative predictor at all time periods post-injury and distinctly predictive of those with the worst outcome (see also Ref. 70). Thus, the mere presence or absence of CT abnormalities on the DOI scan was by itself not much of a predictor of neurobehavioral and or neuropsychiatric outcome, except for those with brainstem lesions. This is consistent with other studies that have attempted to use the DOI CT as a functional indicator of outcome (8, 71–73).

We next examined how DOI CT findings related to more long-term MR imaging findings, using quantitative measures, exploring the relationship of atrophy (i.e., increased VBR) determined at 25 days or later post-injury to outcome. One of the nice factors using the VBR metric is that it automatically corrects for head size differences (74), so no further adjustment in the ratio score is need in comparing subjects of different age, sex or physical characteristics. It may seem intuitive that with greater rating of acute CT abnormality that more prominent VBR would be the outcome. However, this was not the case. It appears that a threshold effect was present, where once injury equalled or surpassed a Marshall et al. (65) Level II rating (see Table 15-2), significant cerebral atrophy resulted that was indistinguishable from the other CT ratings. Another way of saying this is that once a Level II CT classification had been reached, DBI effects had occurred that ultimately resulted in generalized cerebral atrophy, but the degree of cerebral atrophy was rather independent of the CT rating. Interestingly, in the Katz and Alexander (8) study, presence of scan abnormalities, in association with the length of PTA, was the best predictor of outcome (see also 75). Again, it may simply mean that it is not so much the magnitude of DOI CT scan abnormalities, but rather the mere appearance of abnormalities in conjunction with certain markers of brain injury severity, such as PTA, that become predicative of functional outcome. Regardless of DOI CT ratings, by one-year follow-up, increased VBR was associated with greater deficits in FIM and DRS outcome. Presence of any DOI CT lesion has been shown to be associated with greater likelihood of developing MRI identified cerebral atrophy and greater atrophy is a risk factor for worse outcome (43).

When post-traumatic atrophy is substantial, especially in cases where acute injury is a Marshall et al. (65) CT rating of Level II or greater, tracking changes from the DOI CT scan can be most informative, simply by viewing the progression of change in the ventricular system and prominence of cortical sulci in imaging studies (either

CT or MR; see Figures 15-8 and 15-10). Somewhere between 25 days post-injury and six months, the majority of atrophic changes that are likely to occur will have done so (see 40, 76), although degenerative changes may continue for up three years post-injury before the brain returns to its ‘normal’ age-related volume loss (see 77). Given these observations, if the clinician obtains the DOI CT and a follow-up CT or MR scans at least six weeks post-injury, presence of identified lesions or atrophic changes relate to poorer outcome. Suggested methods for easy clinical rating of these abnormalities will be offered in the next section.

In the study of TBI outcome, Dikmen et al. (78) have compiled a variety of measures they label as a “Functional Status Examination” (FSE, 78) that include the Glasgow Outcome Scale (GOS, 79), health and back-to-work questionnaires, psychosocial and emotional functioning, as well as two neuropsychological measures [i.e., Trail Making Test (80), California Verbal Learning Test (81)]. A single FSE composite score can be created from these different measures and then used to explore DOI CT relationships with outcome. Using the FSE, Temkin et al. (72) examined 209 adults with TBI all with CT abnormalities (i.e., 65, rating of Diffuse Injury II or greater) and only 20 percent of the cases reported no problems, which formed their ‘good’ functional status group, meaning that 80 percent had some residual impairment reflected in worse FSE composite scores. The majority of CT abnormalities in this ‘good’ outcome group where Marshall et al. (65) classification group II with regard to DOI CT abnormalities with the majority in the ‘good’ outcome group having GCS of 13–15, but minimal PTA. In contrast, the 80 percent in the Temkin et al. (72) study that had intermediate (i.e., some residual deficit) to poor FSE findings, also had Diffuse Injury II classification by Marshall et al. (65) standards as the most common rating with GCS also in the 13–15 range. They even had similar LOC duration but what distinguished this group with poorer outcome was longer PTA. Thus, long duration PTA and presence of at least a Marshall et al. rating of II, results in the worse functional outcome.

Katz and Alexander (8) examined 243 patients with TBI admitted to an inpatient rehabilitation unit and studied the global effects of abnormalities on either CT and/or MR imaging including petechial white matter hemorrhages, diffuse or localized edema, intraventricular or subarachnoid hemorrhaging, and cortical contusions. All imaging studies were based on clinical ratings of the scans and did not systematically employ the Marshall method for rating CT scans and included not only DOI scans but sub-acute scan information as well. Presence of scan abnormalities in association with duration of PTA was associated with greater deficit as measured by the GOS (79). Interestingly, focal lesions were not that predictive of outcome. Their study also addressed age where older

individuals (i.e., >40 years of age) demonstrated worse outcome even though imaging and injury severity characteristics were not different. Integrating these findings with the Bigler et al. (9) and Temkin et al. (72) studies, discussed above, since of all the injury severity measures (i.e., LOC, PTA, GCS), PTA is the most predictive of VBR (see Figure 15-9) and, since Temkin et al. (72) and Katz and Alexander (8) both demonstrated the importance of PTA in defining outcome, PTA, in relationship to imaging findings, may provide the best indicators of functional outcome. Consequently, worse functional outcome is expected when structural neuroimaging on the DOI scan demonstrates presence of a Marshall et al. (65) level rating of II or greater in conjunction with extended duration PTA or when chronic findings of focal or generalized cerebral atrophy are found on follow-up imaging more than 25 days post-injury.

### CLINICIAN BASED RATING METHODS FOR STRUCTURAL NEUROIMAGING IN PREDICTING FUNCTIONAL OUTCOME

#### Lobular Atrophy and Functional Outcome

For a variety of reasons, including the configuration of the brain within the anterior and middle cranial fossa, frontal and temporal regions of the brain are particularly vulnerable to injury (82), as explained above and exemplified in Figure 15-16. Scheid et al. (83) found the frontal lobes to have at least three times the number of microbleeds than any other brain region, with the temporal lobe coming in second place for most frequent location for injury. This was graphically depicted in the group VBM analysis presented in Figure 15-11 and in an individual case as presented in Figure 15-16, where neuroimaging studies were performed several years after significant brain injury where the patient initially sustained frontal and temporal lobe contusions, leaving the patient with chronic lesions as areas of focal encephalomalacia that also exhibited perfusion defects on SPECT imaging. Because of the critical nature of frontal and temporal regions in regulating memory, executive and emotional functioning, damage to these areas typically affects such functions. A simple lobular rating method has been shown effective in establishing the degree of atrophy in frontal and temporal regions (84) that can be used by the clinician to forecast functional outcome relationships. The ratings are based on T1 weighted MR images, but other weightings could also be substituted, including CT imaging. Figures 15-17 and 15-18 demonstrate this clinical rating method and Figure 15-19 presents actual TBI cases and their functional outcome associated with the clinical rating methods for identifying frontal and temporal lobe atrophy using the guidelines shown in Figures 15-17 and 15-18. In studies that have employed this

method presence of frontal and/or temporal lobe atrophy was chiefly associated with neuropsychological deficits in memory as well as associated deficits in executive function and presence of neuropsychiatric symptoms, particularly depression and anxiety (84, 85). Because these rating methods only require visual inspection of the imaging studies, they can be performed in the clinician's office and provide a useful index for establishing brain-behavior relationships and functional outcome in TBI. One reason for the importance of identifying temporal lobe atrophy is because of the relationship of hippocampal atrophy (86) and the susceptibility of the hippocampus to injury (87).

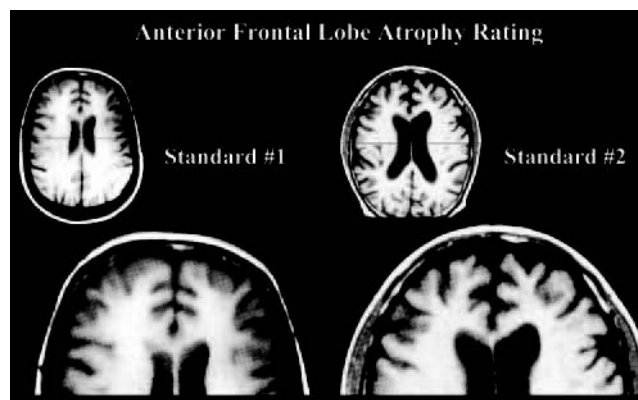


FIGURE 15-17

Anterior frontal lobe atrophy rating of T1-weighted axial images based on the method outlined by Victoroff et al. (117). In performing this rating, the frontal region has been isolated in red as shown in the axial view inset and the rating standards blown-up for the Standard #1 and #2 images. Presence of atrophy is visualized as a prominence in subarachnoid cerebral spinal fluid (CSF), which fills the widened sulci because of reduced gyral size. On the T1 image presented in this figure, CSF is represented by dark signal. Ratings focus on the cortex anterior to the frontal operculum (that is, anterior to the insula). Ratings assess the single image showing the lateral ventricles at the point of the longest visible antero-posterior connection or depending on the slice angle the image closest to the mid point of the genu of the corpus callosum where full view of the extent of the interhemispheric fissure can be viewed, example as shown. Atrophy is rated as follows: 0 = none or negligible (see Figure 15-19, control subject); 0.5 minimal, but less than seen in Standard #1; 1 = mild or moderate = equal to or greater than standard #1, or up to that equal to Standard #2; 2 = severe = definitely more than Standard #2. The key in making these ratings is to not focus on ventricular dilation, focal pathology of the frontal lobes or some other type of abnormality, other than the atrophy. The ratings can either be performed as a total frontal atrophy rating or by left and right. As shown in Figure 15-19, two clinical cases of severe traumatic brain injury (TBI) demonstrate the implementation of the rating in this figure and Figure 15-18



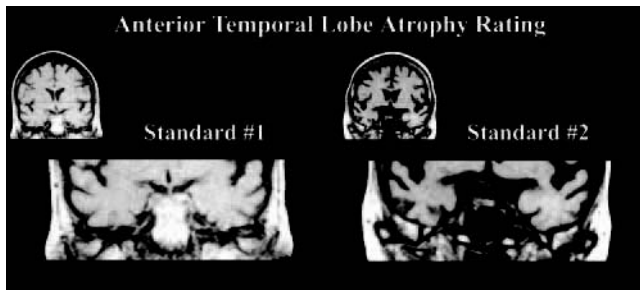


FIGURE 15-18

All of the clinical caveats given in the caption for Figure 15-17 also apply in rating the temporal lobe. Ratings are carried out on the T1 coronal image. Coronal images are used because they provide better visualization of medial temporal anatomy than axial images. Ratings assess the single image that is the first image, moving posteriorly, that definitely shows both temporal stems connecting the temporal and frontal lobes. This image usually shows the amygdalae and/or anterior aspect of the hippocampus (but neither the amygdala nor the hippocampus is rated). Ratings focus on gyral atrophy, attempting not to be influenced by the width of the Sylvian fissure (which might reflect parietal rather than temporal lobe atrophy). To get a total temporal lobe atrophy rating, both individual temporal lobe ratings can be summed. The rating following standards are used: 0 = none or negligible (see Figure 15-19); 0.5 = minimal, or up to that seen in Standard #1; 1 = mild or moderate = definitely more than standard #1, less than or equal to Standard #2; 2 = severe = definitely more than Standard #2. As an example, an actual rating of temporal lobe atrophy in a TBI patient is presented in Figure 15-19

### White Matter Hyperintensities (WMHs) and Functional Outcome

Damage to white matter may show up as a hyperintensity on several types of MR imaging sequences (i.e., T2, intermediate, etc.) and relate to functional outcome (88–91). While such hyperintensities do occur in the normal population, are related to aging (92) and by themselves may not signify pathology (92, 93), they are more frequent in patients who have experienced a head injury (94). There are simple rating scales that can be used by the interested clinician to classify WMHs, typically in periventricular (PV) and centrum semi-ovale (CS) regions of the brain; these are described in Figure 15-20 and several TBI cases with WMHs are shown in Figure 15-21. In the study by Hopkins et al. (94), WMHs in frontal and/or temporal regions were associated with greater deficits in memory and executive function compared to TBI patients without WMHs. Additionally, TBI patients with WMHs endorsed more symptoms of depression and anxiety. The qualitative rating method of WMHs is straightforward to perform, and can be readily done in the clinician's office if the proper image sequences have been obtained. Simply stated, presence of WMHs in frontal and temporal brain regions is

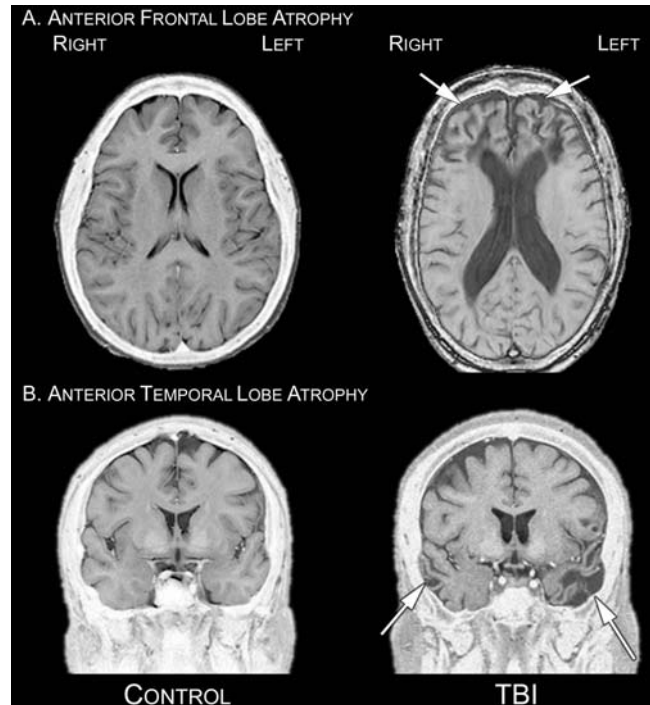


FIGURE 15-19

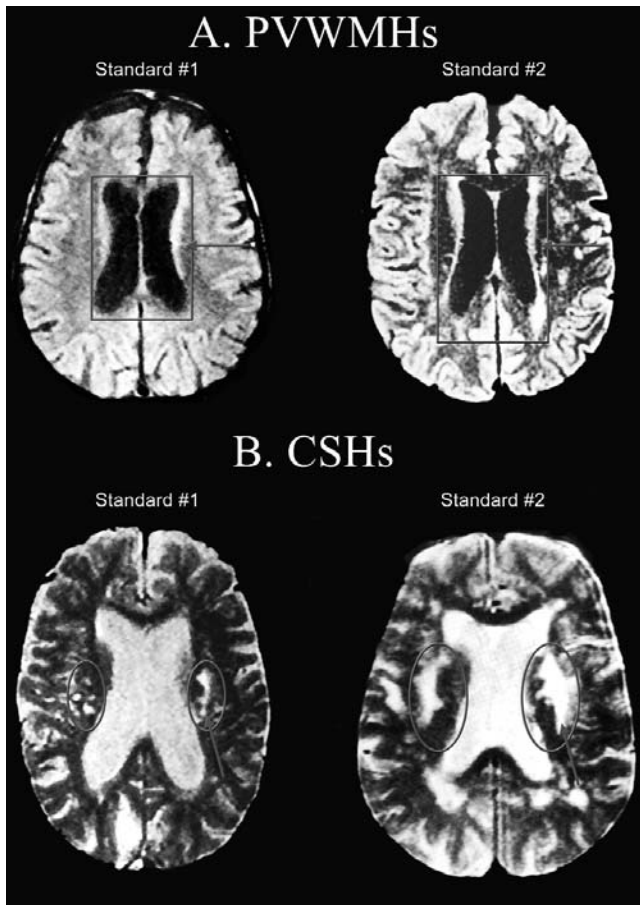
Using the rating method outlined in Figures 15-17 and 15-18, two different TBI patients, one with frontal atrophy (top right) and the other with temporal lobe atrophy (bottom right), were rated. For comparison, two non-brain injured age-matched controls are presented on the left, both received a 0.0 rating on their respective ratings. The frontal rating for atrophy (shown in A) was a 2, bilaterally. Note in comparison to the normal control, the prominence of the frontal sulci and inter-hemispheric fissure. For the temporal rating it was also a 2, but only on the left. It was 1 on the right. Both patients had poor outcome (impaired memory and executive function and at the time of imaging, both had received long-term antidepressant medication for mood management), particularly the one with such prominent frontal atrophy. These type of clinical ratings can be quickly performed on any patient and provide a meaningful qualitative rating for linking structural pathology to functional outcome. Adapted from Bergeson et al. (84)

associated with worse functional outcome in TBI. Since, the degree of WMH abnormality is related to severity of injury, and severity of injury is related to worse functional outcome, presence of WMHs becomes another rating index of severity of injury. The clinical cases using this method as shown in Figure 15-21, where all patients had significant residual neurobehavioral deficits in association with WMHs.

### Clinical Rating of Ventricular Dilation as a Predictor of Outcome

Ventricular dilation, specifically hydrocephalus ex vacuo, as previously discussed, was the first trauma induced





**FIGURE 15-20**

White matter hyperintensity rating methods are presented in this figure. (A.) *Method for rating periventricular white matter hyperintensities (PVWMHs)*: PVWMHs are defined as hyperintensities hugging the ventricle (“rims” and “caps”) on the proton density (intermediate echo) axial image. The proton density images were used in the original Victoroff et al. (117) standardization because these images exhibit good contrast between the ventricles and PVWMHs, although T2-weighted images can also be used. Ratings assess the single image showing the lateral ventricles at the first level (going superiorly) that is definitely superior to the lateral bulges of hyperintensity created by the heads of the caudate nuclei. 0 = none or negligible; 0.5 = less than or equal to standard #1; 1 = mild or moderate = definitely more than standard #1, less than or equal to standard #2; 2 = severe = definitely more than standard #2. Note that in Standard #2, the signal is brighter and more extensive going beyond, in some cases, the length of the ventricle (see double arrow). For the standard, Victoroff et al. (117) used the highlighted image in the figure, rating only the left (views are in radiological perspective.)

(B.) *Method for rating centrum semi-ovale white matter hyperintensities (CSHs)*: CSHs are defined as deep white matter hyperintensities definitely separated from the ventricle on the T2-weights axial image. Hyperintense T2 lesions may be seen with or without corresponding hypointense T1 lesions. When corresponding lesions less than 0.5 cm are seen on both T1

and T2, particularly in the periventricular white matter and basal ganglia, they are regarded as probable Virchow-Robin spaces. Lesions greater than 0.5 cm seen on both T1 and T2 are regarded as probable completed infarctions. Both are excluded from the ratings of CSHs. Thus the CSH rating encompasses all hyperintense T2 lesions that do not have a matching hypointensity on the T1 image, regardless of size, degree of hyperintensity, or shape. Ratings assess the single image showing the lateral ventricles at the point of the longest visible antero-posterior connection. When in doubt, ratings are made by reference to one side (the left side, viewer's right) of the standard scans: 0 = none or negligible; 0.5 = less than or equal to the left side of standard #1; 1 = mild or moderate = definitely more than standard #1, less than or equal to the left side of standard #2; 2 = severe = definitely more than the left side of standard #2. Again, as in A., the standard image is highlighted.

pathological change to be systematically investigated in TBI following the introduction of clinical CT imaging in the mid 1970s (see Refs. 95, 96). Ventricular dilation, as previously explained, is a sign of generalized cerebral atrophy where more dilation is associated with poorer outcome (2, 6). Unfortunately for the clinician, most of the work with ventricular dilation and outcome from TBI has been based on quantitative methods that require digital images along with hard and software for image analysis. However, a simple rating method can be performed, using data already presented in cases used in this Chapter. Since ventricular size is quite constant through the 6th decade of life (41, 97), this makes clinical rating relatively straightforward. Using a four-point scale, as discussed above with lobular atrophy and WMH ratings, where 0 represents ‘within normal limits’, .5 indicates slight dilation, 1.0 indicates mild to moderate and 2 represents moderate and beyond, ventricular dilation can be established by using the standards presented in Figure 15-22. Clinical ratings of 1 or higher are the ones most likely to be related to poorer outcome. Groswasser et al.’s (2) research suggests that this may be accomplished by just rating the III ventricle. Normal III ventricle size is rather slit-like (see Figure 15-23). Because of its midline position deep within the brain, III ventricle dilation may reflect atrophic changes of not only subcortical but cortical atrophy and may be very sensitive to parenchymal volume loss anywhere in TBI (98). Again taking from cases already presented in this chapter, Figure 15-23 shows the ease in viewing III ventricle

Similar ratings can be made using this scheme when fluid attenuated inversion recovery images (FLAIR) and various susceptibility weighted MR images as they too have sensitivity to white matter abnormalities and presence of hemosiderin (as a marker of shear injury) in white matter. Figure 15-21 shows white matter injury with the above ratings in two TBI cases. These ratings can also be applied to white matter abnormalities that are outside the traditional region of the centrum semi-ovale. For ease in classification these are labeled CSH+. An example of this is presented in Figure 15-21

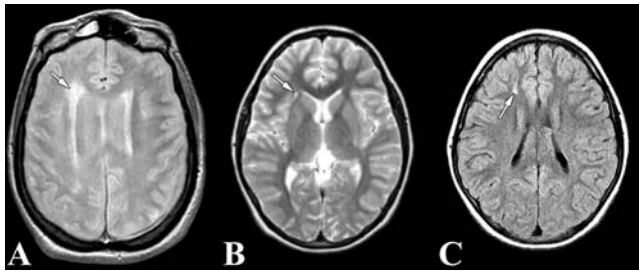


FIGURE 15-21

(A) Axial proton density magnetic resonance (MR) scan showing periventricular white matter hyperintensities (PVWMH; see arrow) in a traumatic brain injury (TBI) patient in the frontal region on the right (scans are in radiological perspective). (B) T2 weighted image showing white matter hyperintensities (CSH+) in right frontal region (arrow). (C) Fluid attenuated inversion recovery images (FLAIR) image showing CSH+ in another region of the frontal lobe in the same TBI patient as shown in B. Presence of these types of frontal lesions relate to impaired functional outcome in TBI and likely reflect focal disruption of white matter pathways and are a clinical manifestation of diminished white matter integrity

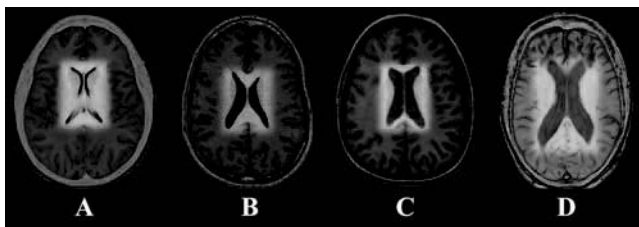


FIGURE 15-22

Using scans from different figures in this chapter, a simple, normal 'Ventricular Size' rating can be established by using the four figures and a four point rating scale. Ventricule Part A is from the control subject in Figure 15-19A. Part B is from the subject in Figure 15-13, although this body of the lateral ventricle view was not actually shown. Part C is from Figure 15-6D and part D is Figure 15-19A (traumatic brain injury, TBI, patient). Similar to the ratings for focal atrophy of the frontal (see Figure 15-13) or temporal lobe (see Figure 15-14) regions, the ventricular rating is based on a 0, 0.5, 1 and 2 rating, where A represents 0, B represents a 0.5 (greater than A but equal to or less than B), C represents a 1.0 (greater than B but equal to or less than C) and 2.0 is anything greater than C exemplified by D. The presence of increased ventricular size in TBI is associated with worse functional outcome

size and its relationship to brain injury severity and outcome.

### Coup-Contre-Coup and Outcome

The coup-contre-coup phenomena in brain injury is a common form of injury (29) and actually represents another

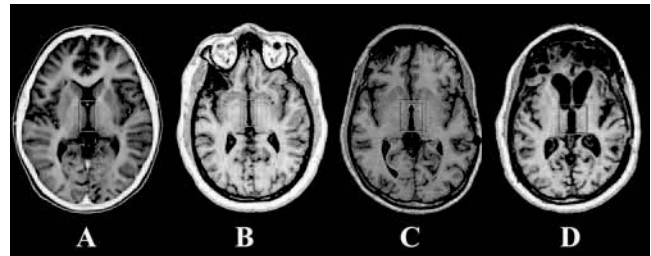


FIGURE 15-23

Using scans from different figures in this chapter, a simple 'Ventricular Size' rating of the III Ventricle can be established. (A) Using the axial MR view from Figure 15-8, with a reversed gray scale image, the III ventricle region is outlined in red. This represents a normal III ventricle size. (B) View (not previously shown) taken from the case presented in Figures 15-3 and 15-6 and shows a mild dilation (III ventricle outlined in red). (C) This view was taken from the case presented in Figure 15-16 and demonstrates a mild-to-moderate dilation (particularly the more posterior aspect of the III ventricle as outlined in red). (D) This was taken from the case in Figure 15-7 and demonstrates a moderate-to-severe dilation of the III ventricle (outlined in red). Applying the four point rating scale for III ventricle dilation A would be rated as 0; B at 0.5; C a 1; and D a 2. In each, classification incorporates the figure as equal to or less than the Standard. Increased III ventricle dilation in traumatic brain injury (TBI) is associated with worse outcome

factor that complicates the prediction of outcome using neuroimaging findings. As previously discussed this is excellently demonstrated in the neuroimaging depicted in Figure 15-5. This patient fell some 20 feet, striking the left frontal region, resulting in depressed skull fracture and development of a subdural hematoma that had to be neurosurgically removed. The residual focal effects of the left frontal injury are readily detected by the presence of focal atrophy, highlighted in red in the illustration. However, only on the FLAIR image, can the contre coup damage be detected in the right parietal area, in the form of abnormal signal intensity, not atrophy, particularly in white matter. The right parietal damage is in a linear path directly opposite the point of left frontal impact, where the skull fracture occurred. Although beyond the scope of full discussion in this chapter, an obvious implication of a contre coup injury such as that shown in Figure 15-5, some 10 cm completely opposite the point of impact, means that tremendous bio-mechanical forces of physical energy were transmitted through the brain on this plane (see Ref. 39). With such impact forces of injury transferred through the brain there typically are widespread microstructural changes within the sectors subjected to acceleration/deceleration injury that are not detected by neuroimaging, but only pathologically identified microscopically (see Ref. 29). With regards to functional outcome in the presence of coup/contre coup injuries, the very nature of these multi-focal injuries in association with DBI factors, makes prognostication difficult. This may

be why in the Katz and Alexander (8) study presence of focal contusions was not strongly associated with outcome. When lobular atrophy is identified, as discussed above, additional imaging sequences should be obtained to explore whether contre coup injury is present and its relationship to functional outcome.

### TBI, Anterior Commissure and Basal Forebrain Damage

Over the last decade, the clinical importance of the basal forebrain in neuropsychiatric disorders has been clearly established (99, 100) and discussed earlier in this chapter. As the name implies, the basal forebrain is a region at the posterior base of the frontal lobe, cradled in the anterior cranial fossa, situated just above and anterior to the clinoid process of the skull, making it vulnerable to impact injury at the skull-brain interface in this region (101). The location of the anterior commissure (AC) is typically considered part of one of the superior boundaries of the basal forebrain. The AC is comprised of a small band of white matter tracts that course between the two hemispheres that interconnects mesial temporal and orbitofrontal cortices (102). Although not specifically investigated, it probably shares a similar vulnerability as does the CC (103) and as recently shown by Wilde et al. (43) the ventral aspect of the frontal lobe is particularly vulnerable to injury. As shown in Figure 15-24 (this is the same patient as shown in Figure 15-16), in comparison to a normal control, a TBI patient with severe injury clearly demonstrates AC atrophy, as shown by the dilation of the suprachiasmatic recess compared to the control subject. What is also evident in this illustration is that all of the area under the AC exhibits atrophy as well. This region contains the critical origins of cholinergic innervation for all of cerebral cortex (104). The AC has traditionally been considered part of the upper boundary of the basal forebrain, so atrophic changes at the level of the AC and below, probably reflect basal forebrain damage. The basal forebrain regions at the AC level comprise critical structures of the limbic system and the ventral striatum including the extended amygdala, the basal nucleus of Meynert and the midline septal nuclei (99, 100). These brain regions have been shown to be critical for maintenance of emotional regulation and given its vulnerability to injury; it is likely that basal forebrain damage contributes to the common emotional changes associated with TBI (62, 105, 106). Lastly, as shown by the VBM analysis depicted in Figure 15-11, one of the areas of greatest change in gray matter density in this cohort of TBI subjects analyzed was in the basal forebrain region.

### Medial Temporal Lobe Damage

As shown in Figure 15-13, the medial aspect of the temporal lobe butts up against the medial surface of the

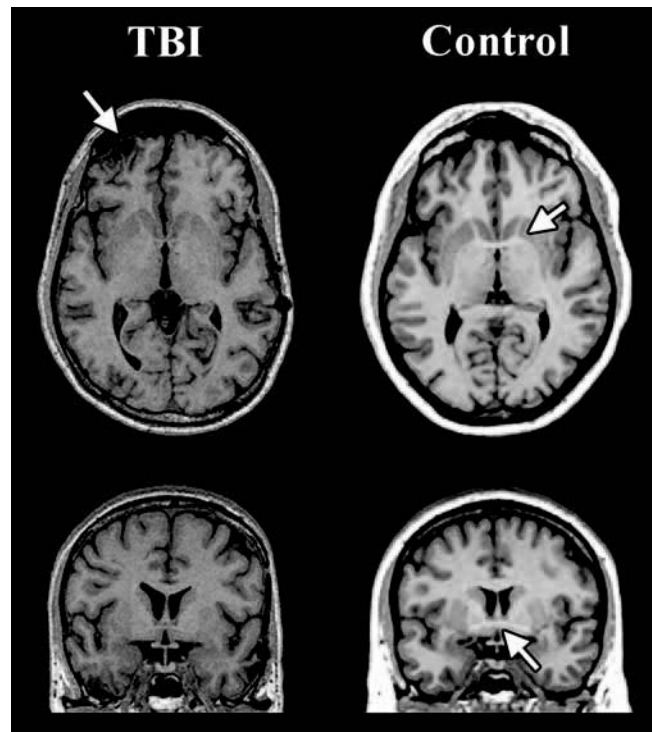


FIGURE 15-24

The TBI case on the left is the same as shown in Figure 15-16 and Figure 15-23C. The control subject on the right is the same as shown in Figure 15-6A. The arrows shown in the control subject point to the anterior commissure (AC) in axial (top right) and coronal (bottom right) planes, that is easily identified by the distinct and unmistakable band of white matter fiber projections. In the coronal view, the region beneath the AC, in part, defines the basal forebrain. In comparison to the TBI subject, it is clear that there is a diminution in the size of the AC. Also note in the TBI patient dilation of the III ventricle (see Figure 15-23) and enlargement of the suprachiasmatic recess, indicating volume loss of brain parenchyma in this area. The suprachiasmatic recess is just to the left margin of the arrow in the bottom coronal view of the control subject and is situated just above the optic chiasma. This is also the region of the substantia innominata, where in the nucleus basalis of Meynert exists and other critical structures of cholinergic innervation (121, 122). This TBI patient also had an area of focal encephalomalacia of the frontal region (arrow), as indicated by increased focal CSF in that region. Damage involving atrophy of the AC and inferior frontal region, including the basal forebrain likely results in significant changes in memory and mood regulation, as was the case with this patient

middle cranial fossa, formed in part by the clinoid and sphenoid bones. The medial surface of the parahippocampal gyrus houses both the entorhinal cortex and subiculum, which input the hippocampus. Hippocampal atrophy following TBI has been one of the most replicated findings in quantitative analysis of temporal lobe

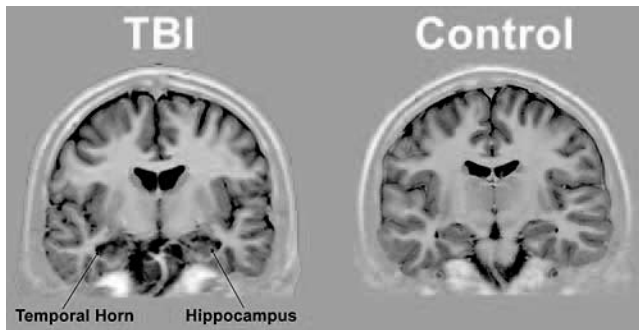


FIGURE 15-25

True inversion recovery sequence that highlights the distinction between white and gray matter and clearly shows the atrophy of the medial temporal lobe, expressed as reduced volume of the hippocampus (compare to control subjects at similar level) and temporal horn dilation. Loss of medial temporal lobe volume, and in particular volume loss of the hippocampus, gives rise to 'downstream' atrophy of the limbic projection system of the fornix, as shown in Figures 15-26 and 15-27

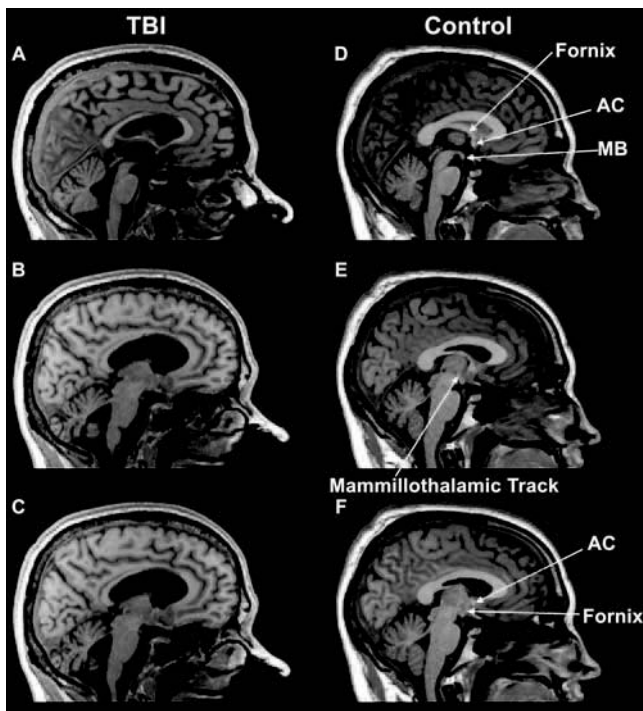


FIGURE 15-26

As labeled in the control subject, atrophy of the fornix, anterior commissure (AC), mammillary body (MB) and the mammillothalamic track can be readily identified in the TBI patient. The sagittal image is from a 3 Tesla scan and clearly shows ventricular dilation, thinning of the corpus callosum, marked shrinkage of the fornix, clear reduction in the size of the AC and MB with no ability to identify the mammillothalamic track. This patient sustained a severe TBI in a MVA, with his initial GCS rated at a 5

structures (63), but as shown in Figure 15-13, the atrophy of the medial temporal lobe and its underlying white matter pathways exhibits atrophy as well as the distinctly evident hippocampal atrophy. While memory outcome is one of the most replicated of the neurocognitive sequelae of TBI and relates to hippocampal atrophy (60), memory impairment following TBI could result from widespread medial temporal lobe damage as well (see Ref. 62). As shown in Figure 15-25, even though the hippocampus is clearly atrophic, so is entorhinal cortex and adjacent white matter. Since entorhinal cortex is the recipient of diverse inputs from all regions of cerebral cortex, the disruption of memory may have nonspecific factors associated with damage outside of the hippocampus, proper and this likely relates to only the modest relationship between hippocampal atrophy and memory outcome. Damage to the medial temporal lobe structures and the hippocampus, in turn disrupts input to the fornix, resulting in atrophy of the fornix, which may also be susceptible to mechanical deformation and shear/stretch effects as well (107), can be readily visualized in MR imaging as shown in Figures 15-26 to 15-27. Furthermore, fornix atrophy leads to reduced size of the mammillary body and the mammillothalamic tracks, as shown in Figure 15-26 and 15-27. Returning to Figure 15-14, all of these structures are critical to memory function and susceptible to injury in TBI.

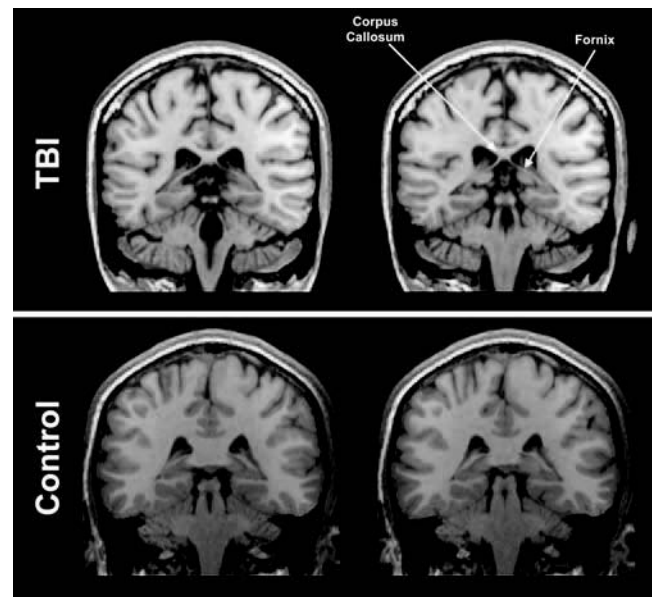


FIGURE 15-27

Fornix in coronal perspective as it comes off of the posterior aspect of the hippocampus at the level of the splenium of the corpus callosum. This patient sustained a severe TBI in a MVA where her initial GCS was reported to be a 4. This illustration demonstrates the ease with which fornix atrophy can be identified

### THE INTEGRATION OF STRUCTURAL AND FUNCTIONAL IMAGING

The image of the brain generated by CT or MRI only represents gross brain structure. Although in the living individual structure is never devoid of function, neither CT nor MRI structural imaging provide a direct measure of function. However, as explained in Chapter 12 on functional imaging in this book, the principles of structural imaging can be applied to obtain functional measures of the brain. As already discussed, when structural changes are detected they merely depict where the macroscopic abnormalities are and not necessarily the totality of areas or systems that may be disrupted. However, structural imaging typically represents the very best method for projecting functional changes as nicely depicted in Figure 15-28 based on the studies by Lewine et al. (26, 49). As shown in this illustration, MR structural imaging is used as the format for demonstrating where SPECT and MEG abnormalities were found, both measures of functional impairment. As depicted in Figure 15-28, structural pathology in the inferior frontal region was obvious on MR imaging, likely from gliding-type contusions between the brain and the inner table of the skull, particularly the greater sphenoid and the bony protrusions of the interior surface of the frontal bone (i.e., crista galli). Despite the clarity of these distinct lesions, with relatively well demarcated boundaries as defined by the MR signal intensity returning to uniformity once outside the confines of the lesion, neural function was not normal in the 'normal' appearing tissue just outside of the well defined areas of damage. As such, these 'normal' areas, even though close to the lesion, do not exhibit abnormal MR signal and therefore, from strictly a structural imaging standpoint, would be interpreted as 'normal' brain parenchyma. However, when the perfusion defects of SPECT are superimposed, it is apparent that the area of dysfunction exceeds the distinct MR identified lesion boundaries. In other words, the actual area of 'damage' that disrupts function, as measured by SPECT imaging is greater than the lesion(s). More importantly, though, the SPECT abnormalities still do not encompass all the abnormalities as reflected in the MEG findings. Therefore, the true extent of the 'abnormality' will always be larger than the defined lesion. By integrating all three methods, MR, SPECT and MEG, a clearer picture of more generalized cerebral dysfunction involving a much larger area of cerebral cortex emerges. It may be that such integrated imaging methods will yield better prediction of functional outcome. Using the same type of techniques, essentially any imaging modality can be integrated with another, such as 3-D CT or MR images integrated with PET, MRS, quantitative EEG data and so forth. An example of this is presented in Figure 15-29 showing the presence of structural atrophy of the medial temporal area in

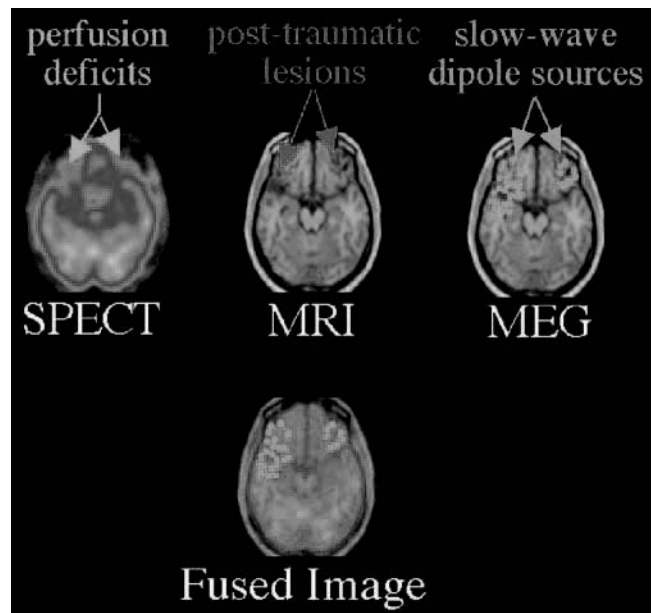


FIGURE 15-28

Data are shown for an 18-year-old male subject who suffered moderate head trauma in a motor vehicle accident at age 14. The subject had a Glasgow Coma Score (GCS) of 10 at the time of hospital admission. This patient sustained a moderate-to-severe traumatic brain injury (TBI) with post-injury neuroimaging being performed more than a year post-injury. The single photon emission computed tomography (SPECT) and magnetoencephalography (MEG) were co-registered with the coordinates of the magnetic resonance imaging (MRI), so that all three images could be reliably integrated where SPECT and MEG abnormalities are projected specifically on their corresponding regions on the MRI, as shown in the top row. This also permits the 'fusing' of all images, into a single integrated image showing all abnormalities in a single view. Normal SPECT perfusion is characterized by yellow-orange, more prominently observed toward the cortical surface, where gray matter is found. Blue represents less to absent perfusion, normal in regions of highly concentrated white matter (do to minimal metabolic activity in such regions) or in cerebral spinal fluid (CSF) filled spaces, because no perfusion occurs in such regions. Initial MR revealed by frontal and left temporal contusions and a left fronto-temporal sub-dural hematoma. At the time of SPECT/MRI/MEG imaging, the patient had a chronic post-concussive syndrome characterized by mild depression, frequent head aches, memory and attention problems, and general cognitive decline as characterized by low IQ and impaired processing speed and accuracy. MRI revealed focal bi-frontal and left temporal encephalomalacia, some generalized atrophy and ventricular dilation, and evidence of diffuse axonal injury. SPECT showed concordant hypoperfusion of right and left frontal regions and the left temporal lobe. SPECT also provided evidence of a mild generalized cortical atrophy and ventricular dilation. MEG revealed focal slow waves at concordant right and left frontal and left temporal regions. MEG also showed left parietal slow waves. MEG was the only imaging method to explicitly reveal parietal injury. (Reproduced with permission from Lewine et al., Ref. 26.)

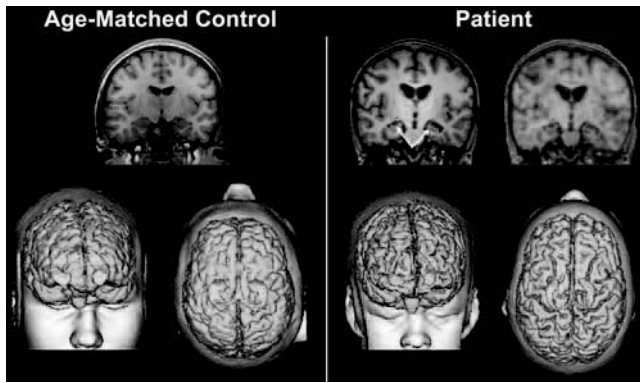


FIGURE 15-29

The T1 coronal image of the TBI patient presented on the right clearly demonstrates bilateral hippocampal atrophy (arrows) clearly defined by the shrunken appearance of the hippocampi and the dilated temporal horns of the lateral ventricle. The Fluorine-18 dioxylucose (FDG) PET imaging fused with the structural MRI, as shown on the right demonstrates relatively normal cortical metabolic activity, except in the medial temporal lobe region and particularly in the bilateral hippocampal region. The hippocampus can be isolated in 3-D as shown below, where the control subject demonstrates the normal appearance of the hippocampus whereas in comparison to the patient's atrophic hippocampus. As would be expected, this patient exhibits significant deficits in short-term memory function, where some of his neuropsychological scores are below three standard deviations of where they were expected to be prior to injury

a child who sustained a severe TBI that resulted in bilateral hippocampal atrophy. Interfacing the PET imaging with the structural clearly shows significant defects in cerebral activation in the medial temporal region, that is actually asymmetric even though the appearance of the structural atrophy of the hippocampus and temporal lobes appear to be symmetric and bilateral.

### NEW TECHNIQUES AND INTEGRATION ACROSS TECHNIQUES: THE FUTURE OF STRUCTURAL IMAGING IN PREDICTING FUNCTIONAL OUTCOME

Only a brief statement will be made on this topic, which should be obvious to the reader at this time. Detection of structural pathology will only improve with the introduction of new hardware and software for structural image analysis (1, 108–114). More rapid and automated image analysis methods are being introduced on a regular basis (115). Accordingly, the prediction of functional outcome in TBI will only improve in the future, particularly as functional imaging measures are integrated with structural (116).

## SUMMARY AND CONCLUSIONS

Although predicting functional outcome from neuroimaging findings is a complex task fraught with many limitations, recent advancements in brain imaging have resulted in significant improvement and understanding of the relationship between structural neuroimaging findings and outcome. As a conclusion to this chapter, the following simplified outline is proffered as a clinician's guide in determining relationships between clinical neuroimaging findings and outcome. The rating begins with the DOI scan, typically a CT, compared to various CT and or MR follow-up scans, particularly more than 25 days post-injury.

1. If the DOI CT is a Level I according to the Marshall et al. (65) rating method (no discernible abnormality, as shown in Table 15-1) and there was minimal or no LOC or PTA and GCS was  $>13$ , structural neuroimaging will likely be interpreted as "clinically" normal and neither qualitative or quantitative analyses will be that predictive of functional outcome. In other words, a 'normal' scan does not necessarily mean normal or a good recovery but absence of abnormality, particularly with minimal PTA, tends to be seen in those with the best chance for good functional outcome.
2. If the DOI CT is a Level I but there is positive LOC and PTA, the patient should have follow-up MR imaging (a minimum of 25 days post-injury) that includes protocols sensitive to blood byproducts, white matter integrity and CSF filled spaces. Normal scan findings at follow-up imaging will be predictive of better outcome than found in those with positive follow-up scans. Those with MR abnormalities in follow-up who show enlarged VBR as a sign of generalized atrophy, presence of focal frontal or temporal lobe atrophy or generalized white matter atrophy (i.e., callosal atrophy) or WMHs will have worse outcome. Functional neuroimaging may be particularly important in understanding outcome at this stage.
3. TBI patients with Level II CT findings or worse generally are more likely to have abnormalities identified on follow-up MR imaging and the degree of VBR identified atrophy will relate to outcome. More atrophy (i.e., larger VBR), generally the worse the outcome. Focal atrophy of the frontal and or temporal brain regions will relate to deficits in short-term memory and/or executive function and likewise, will be associated with a greater likelihood for neuropsychiatric disorder, particular in the domain of mood and anxiety based symptoms.
4. Independent of DOI CT rating, in TBI cases where frontal and or temporal lobe atrophy is identified and/or presence of white matter lesions and/or blood

byproducts (i.e., hemosiderin) in these region, using the method outlined in this chapter for rating of lobular atrophy and/or WMHs [i.e., based on the Victoroff et al. (117) method] will be associated with greater deficits in one or all of the following functions: executive, emotion and/or memory. Where focal atrophy is present, review of the scans for potential contrecoup injury is recommended. Presence of contrecoup injury complicates the prediction of functional outcome.

5. Presence of brainstem lesions on DOI CT carries the worst prognosis for functional outcome.

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# 16

## Functional Assessment in TBI Rehabilitation

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**C**hronic disease and injury often result in difficulties performing day-to-day activities, because of physical, cognitive or emotional impairments.

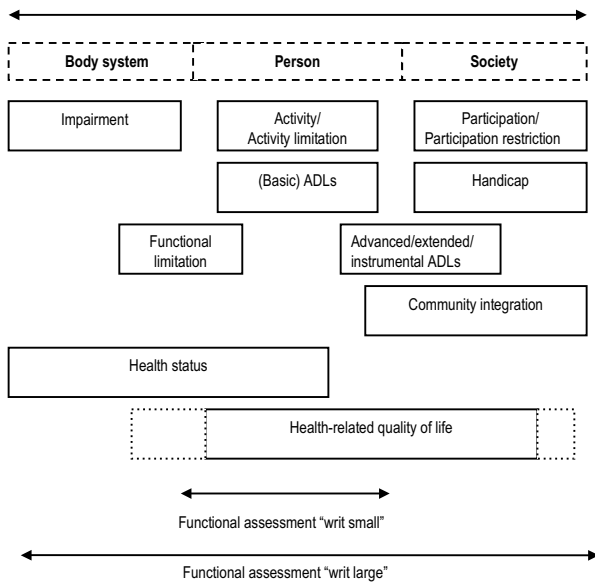
The process of determining the type and degree of such problems, or the ability to perform normal acts, activities and roles, is typically designated “functional assessment”. This is a misnomer, in that “assessment of function” or “functioning assessment” more clearly expresses the nature of this activity. Terms that overlap with “functional assessment” (FA) to a considerable degree are health status assessment, disability assessment or measurement, geriatric assessment, and others (1, 2). All of these activities aim to measure to what degree the person in his or her functioning deviates from “normal”, where normal may refer to typical for persons without disorder (either all persons, or persons of the same age, gender, education, etc.), or the person’s own pre-injury status.

Assessment in this context refers to quantification, where the exact position of the person on a continuum ranging from unable (complete lack of function) to very able (on a level with or even better than “average” or pre-injury) is determined and expressed in a number. This is the meaning of the term FA as commonly used in health care and rehabilitation practice and research. (From other perspectives, quantification is a more limited activity than assessment) (3). However, the term assessment has a second meaning, referring to evaluation or valuation: the

worth or meaning attached to the (amount of) function, by the person involved or by others. While the two types of “functional assessment” are strongly connected, the two are not synonymous. Whereas it is generally true that the value of a particular status increases with functional ability (being able to walk fast is more valuable than being able to walk only slowly), people may differ in how they value one ability compared to another (talking vs. reasoning), and in how they value one specific level of an ability compared to another level (4). These inter-individual differences come into play more, to the degree that the issue shifts from basic human functions (e.g. grasping) to more complex ones (holding down a job). Traditional methods of FA deal exclusively with the quantification issues (which are far from simple by themselves), and not with the valuation question. However, it is becoming increasingly clear that in order to assess with any level of adequacy what medical care and rehabilitation “produce”, issues of valuation need to be dealt with (5). In this chapter, the reasons for and some methods of capturing the subjective valuing of functional states will be discussed, along with more traditional “functional assessment” methodologies and measures.

### THE DISABLEMENT CONTINUUM

As suggested above, “functioning” may cover an extremely broad area, from simple functions involving a single body



**FIGURE 16-1**

Aspects of functioning on a continuum

system to complex activities that are dependent on multiple physical and cognitive skills and are implemented in social interactions according to established social and cultural patterns. In Figure 16-1, the World Health Organization's International Classification of Functioning, Disability and Health (ICF) is used as a framework to delineate various concepts and terms encountered in the FA literature.

The WHO defines impairment as “problems in body function or structure as a significant deviation or loss”; in spite of the word “body”, impairments include deficits in psychological functions (6) p.12. In a previous edition of the ICF, the International Classification of Impairments, Disabilities and Handicaps (ICIDH) (7) the same term was used; the taxonomy offered, however, did not make a clear distinction between deficits of structure and deficits of function at the impairment level. An FA instrument at the Impairment level often used in TBI care and research is the Glasgow Coma Scale (GCS) (8). At the level of the person, activity is characterized as “execution of a task or action by an individual”(6);p.14 its negative aspect, activity limitations, is defined as “difficulties an individual may have in executing activities”(6);p.14. The ICIDH used the term “disability” for this concept, which was defined very much similar to the current term “activity limitation”. Within rehabilitation, the prototypical measure of activity limitations is the Functional Independence Measure (FIM) (9), but many other instruments have been used, within and outside traumatic brain injury rehabilitation. Finally, the person-in-interaction with others may have participation restrictions, which are defined as “problems an individual

may experience in involvement in life situations”(6)p.14; the positive counterpart is characterized as “involvement in a life situation”;(6)p.14 In the ICIDH the term “handicap” was used for the negative aspect, which was defined in a manner quite different from the newer term. However, many of the measures developed to operationalize “handicap”, such as the Craig Hospital Assessment and Reporting Technique (CHART) (10) are now used as measures of participation restrictions, including in the traumatic brain injury (TBI) literature.

Human activities range from simple acts such as stretching a leg to complicated pursuits such as running a household, and it is difficult to define the three concepts of impairment, activity (limitation) and participation (restriction) in a clear and non-overlapping way. The ICF offers separate concepts for the three domains of the disablement continuum, but only two taxonomies: one for Impairments, and one for Activities and Participation, with guidelines for users of the latter as to how the theoretical distinction might be implemented in practice, using the taxonomy. In some instances, it is even not simple to place any one act or activity in one of the three ICF baskets. Many measures of “functioning” such as the Disability Rating Scale (DRS) (11) overlap two or three of the concepts – intentionally or because the developers were not aware that the indicators they combined belonged to distinct conceptual classes.

FA “writ small” deals with Activities/Activity Limitations, and rehabilitation and other specialists have developed many measures to quantify self-care, mobility, everyday communication and other types of activities. We will focus on a limited number of measures commonly used in TBI services and research, but try to give the readers an overview of the concepts and techniques useful in understanding and evaluating instruments, and selecting them for clinical and research applications. FA “writ large” also includes measuring Impairments and Participation (12), and instruments that quantify those aspects of the latter two that are of relevance to TBI are included here.

Many terms developed prior to or outside the ICIDH/ICF can be placed on the same disablement continuum, as shown in Figure 16-1. The core interests of rehabilitation, Activities of Daily Living (ADLs) (sometimes designated basic ADLs) coincide with Activities. Extended (Instrumental, Advanced) ADLs (measured using e.g. the Frenchay Activities Index (FAI) (13) or the Adelaide Activities Profile (AAP) (14)) are generally defined to straddle the Activity-Participation distinction; on the other side of the continuum, Functional Limitations typically represent activities such as grasping and lifting that cross the divide between Impairments and Activities. Measures of Functional Limitations used in TBI care and research include the TEMPA(15) which assesses upper limb function. Developed and applied

outside of TBI care are such UE measures as the CUE (16), and newer LE measures such as the WISCI (17). Community integration instruments, such as the CHART or, in TBI research more frequently, the Community Integration Questionnaire (CIQ) (18) quantify aspects of IADLs, and other facets of Participation, with emphasis on the social interactional components.

Health status, a term used by health outcomes researchers, typically is defined and operationalized as combining elements of Impairment and Activity Limitations, although some measures (such as the well-known Short-Form 36) (SF-36) (19) also includes indicators of Participation. The SF-36 now increasingly is used as a measure of quality of life (QOL). QOL has been defined in a number of ways;(20) most definitions and operationalizations of health-related QOL (HRQOL) overlap with Activities and Participation, and may even take in some aspects of Impairment. Many disease-specific HRQOL measures include symptoms, which typically are missing from Activity and Participation measures; however, many symptoms can be seen as Impairments, which suggests that HRQOL is somehow synonymous with “disablement”, the term the ICIDH’ authors used to represent the entire spectrum from Impairments through Handicaps.

### THE STRUCTURE OF FUNCTIONAL ASSESSMENT INSTRUMENTS

At the simplest level, FA measures consist of a number of separate items, each one of which refers to a narrow or broad ability or skill – for instance, lifting overhead, transferring into a bathtub, or making telephone calls. On each item from two to as many as seven different levels or categories of “ability” are distinguished, which have quantitative values from 0 (or 1) to the highest. The lowest category corresponds to no ability/cannot do at all/need maximum help, and the highest to independence, “normal”, or even above average. Additional metrics have been used, such as difficulty (21) and time needed (22). For measures of participation, metrics used include frequency of performing an activity (10), hours spent on an activity (23), share of activities performed (24), and others. The numbers a patient or subject receives on the constituent items typically are added together, and the total (with or without further arithmetical manipulation) reflects his or her functional status in the domain being measured. For some measures, the items all have the same number of steps and the same minimum and maximum value (e.g. FIM), but that is not necessarily the case – for instance, the Barthel Index(25) consists of some items with only two categories of ability, while the others items have three. Differential scoring of the categories from one item to the next can be used to express the relative

weight (importance) of the constituent skills for overall functioning, according to the instrument’s creator. A separate weighting step prior to addition can be used to achieve the same purpose.

The numeric values of the categories (item scale steps) represent measurement on an ordinal scale – they only indicate relative order along the able-not able (or not participating-participating) continuum, but the differences between scale steps are not equivalent, and the values chosen for them are arbitrary. As a result, adding up the scores for the items to obtain the total score is not an operation that is allowed, based on the rules of mathematics. Therefore, total scores do not reflect position along a continuum that has a true zero point, and constant distances between scale points. (These constitute the definition of a ratio scale, which is what is required for calculating means for a group, or percentage improvement over time). However, research has shown that if the item category values are chosen “reasonably”, the sum of ordinal items corresponds quite well to values on a true ratio scale, at least for intermediate levels of the continuum of total scores (26). Rasch analysis, a mathematical procedure based on Item Response Theory (IRT) has been used to transform a set of scores on ordinal FA items into a score on an interval scale (10, 21, 26). The theoretical assumptions and mathematical manipulations underlying Rasch Analysis-based FA instruments are beyond the scope of this chapter; good introductions to the technique and its application to FA may be found in Bond and Fox (27).

However, most FA measures used in TBI clinical services and research such as the GCS, DRS, and CIQ have never been subjected to Rasch analysis, let alone rescored on the basis of the findings of such an analysis. They may not be unidimensional, and increases from very low initial scores (e.g. a FIM total of 40) may be much easier to accomplish than apparently equally great increases (as expressed in score points) from medium or high starting points (e.g. a FIM of 90). As a result, one should be quite careful in interpreting FA instrument scores as applied to individuals, and to groups. Especially “percent improvement” and “change efficiency scores” should be considered as nothing but approximations of the mathematical precision they appear to offer. Calculation of means and all other operations that require interval scales (regression analysis, etc.) are somewhat less suspect, but the results also should be considered as approximations. Mathematical wizardry cannot make up for the basic problems created by ordinal measurement of skills and performances. In the years to come, more information on Rasch-analysis or IRT analysis of existing FA instruments will become available, and new instruments will be introduced that were developed using up-to-date IRT methods. We will be much more justified in treating the scores on those types of instruments as ratio scale numbers.

## ISSUES IN FUNCTIONAL ASSESSMENT

### Capacity and performance

Two aspects of functioning are commonly distinguished: capacity and performance (6). Capacity is what people can do under optimal circumstances – well rested, encouraged to their best, in a physical environment with minimal barriers. Performance is what they do in everyday life. People who can do self-care not necessarily always do it, for a variety of reasons. One of the most common reason is that their environment is not accommodating, or that the energy and time a task requires preferentially are spent on other, more worthwhile endeavors – whether that is work or watching one's favorite soap opera. Studies with spinal cord injury patients have shown that many for whom self-care is a "marginal" skill prefer to have a personal care attendant or family member perform their care, so that they can get out of the house and get to their job (28). There are no clear parallels for cognitive-communicative skills after TBI, although it is likely that people with limited short-term memory and impaired ability to focus may leave it to others to read a bus schedule for them and tell them what time they need to catch the bus to make it to an appointment, even though with sufficient time and effort they could figure that out by themselves.

At the Impairment end of the disablement continuum, functional limitations tests tend to be performance focused. The ASIA motor scale(29) is based on the patient's ability to contract key muscles, and the physician and patient are hardly interested in the patient's actual frequency of contracting those muscles. At the other end of the continuum, measures of participation or community integration without exception quantify performance. It is either impossible to test capacity (how could one test "ability to function as a brain surgeon"), or not of interest: actual performance is of importance as the long-term outcome of rehabilitative efforts, not potential. It is in the middle ground, the domain of Activities, that a discrepancy between capacity and performance is most likely to be relevant, and performance is modifiable with environmental and other interventions.

### Testing, observation and reporting on performance

Three methods are used to collect functional information. Testing involves requiring the patient or client (or research subject) to perform specific tasks or skills under the direct supervision of the test administrator, who times the test, assesses the amount of help from aids or aides that is needed, etc. This tends to occur in laboratory situations, but testing can also be done in the person's home or other setting where the activities involved are or should be performed (30). Depending on the degree to which the test situation approximates an optimal one, the resulting score

quantifies optimal capacity, or capacity in the situation that is considered most relevant to the uses to which the functional information is to be put.

Observation of actual behavior is the basis for quantifying what the person does do, rather than what he or she can do. Most functional assessments of Activity reported as part of inpatient or outpatient rehabilitation programs is observation based – at least in theory. For instance, the Uniform Data System (UDS) FIM admission and discharge scores are based on what the patient does in the first three days after admission or the last three before discharge. In practice, there is continuous pressure on the patients to perform at their best, especially in treatment with PTs and OTs, and the measure of performance turns into a measure of capacity. Research using the LORS, for instance, has shown that scores reported by therapists are systematically lower than those reported by nurses (31). Nurses presumably report on what they observe the patients doing when going about their life on the nursing unit, while therapists only see them during scheduled hours, where they cannot waste time observing what the patients do naturally – the therapists need to optimize the patients' performance.

A third way of collecting FA information is through report by the patient, or a proxy such as a family member. These reports can involve capacity (for instance, in the CUE(16)), but more typically address performance. Questions are asked about how the person performs the various activities included in the FA measure in his or her daily routine. Using a standardized branching questionnaire, trained interviewers can reach a high-level of inter-rater (inter-interviewer) reliability. This is how data are typically collected for follow-up assessments in the UDS, and other program evaluation approaches.

All three methods have their advantages and disadvantages, in terms of cost, personnel needed, required ability of the patient to cooperate with the data collection, etc. If capacity data are of interest, testing is the preferred method; for true performance data, interviewing is the only feasible approach. Problems arise when the data obtained by two methods need to be linked. For instance, a typical question (clinically and in research) is whether the person manages to maintain or even improve on the skills he or she was discharged with from inpatient rehabilitation. The hospital data are typically collected using observation, in an environment that tends to be more accessible than the typical residence, and with overt or covert pressure to perform one's best. The home follow-up data are normally collected using interviews, concern performance in a different environment, in which there may be no incentive at all to use all the abilities taught in rehabilitation. If a change in functional performance is noted, is this due to the change in data collection method per se, or due to changes in the environment, or even because of changes in the true underlying capacity (continued

neurological recovery)? This issue has hardly been studied, and we don't know enough about differences in scores for various data collection methods for various FA instruments to tease apart the various factors (32).

### The nature of the items

In an IQ test, the person tested completes multiple arithmetic, similarities, and other items which in themselves are not of interest to the test administrator. The IQ score that results is of interest, because it gives an (imperfect) indication of the person's overall cognitive abilities. The focus is on the underlying trait – intelligence. In FA, however, the items most likely have intrinsic meaning, to the person performing the assessment and to the individual assessed: they reflect activities that are of importance in and of themselves – whether it is stair climbing or the ability to communicate a simple idea. FA “tends to occur within a realistic setting that approximates the one in which the actual criterion behavior will occur” (2) p101. That does not mean that there is no underlying construct “functional ability” that is of interest – but the underlying ability is of concern mostly because it informs on the functional items that were part of the assessment, and possibly on those that were not part of it. Because the primary interest is in the items (tasks, activities) themselves, there always is a tendency to include in FA measures the full panoply of acts that are part of normal human functioning. The Patient Evaluation and Conference System (PECS) in one of its versions included 97 items, of which as many as possible were to be completed as applicable to the patient (33, 34). Such an extensive menu is feasible when various staff report on patient status within their area of expertise (speech and language, neuropsychology, chaplaincy, etc.) but not in situations where subjects are tested, or are required to report on their performance. Maintaining a balance between feasibility and inclusion of those functional tasks that are key to living has always been a balancing act for FA instrument developers. Measures that cover “all areas of life” (or at least all aspects of Activities and Participation) tend to select fairly broadly defined tasks (e.g. “dressing”), and limit the number to 10 to 20. Instruments developed for use by specific disciplines are apt to include more narrowly defined tasks (“putting on a pull-over”) and include a large number: The Klein-Bell ADL Scale contains 170 items to cover just six areas: dressing, mobility, elimination, bathing/hygiene, eating, and emergency telephone use (35).

When the focus of FA shifts from performance of individual tasks to the status of broad underlying abilities (“self care”; “motoric strength and coordination”), the need to include each and every possible item diminishes. Traditional psychometric methods can be used to show that the underlying construct can be measured with one set of items (indicators) as well as with another set,

and that the resulting total scores will have high correlations with one another. Some measures of functional limitations (the transition area between Impairments and Activities) do not attempt to “cover the waterfront”; they select activities that are representative of the entire universe of relevant items, and use those to score, for instance, upper extremity functioning. After all, once it is known how much difficulty a subject has picking up a can of soup, and how much picking up a ream of paper, it should be fairly clear how well she would do lifting a paperback book. To what degree this same reasoning applies at the other end of the disablement spectrum, Participation, is not yet known. The ICF distinguishes about 90 different aspects of “Participation”, in 9 chapters covering communication, mobility, domestic life, etc. Is it necessary to obtain information on all of these to get a complete view of someone's level of Participation? Or is it possible to extrapolate from three household tasks to all others, and also to know quite adequately how well the person does in the civic responsibilities domain? That depends to a large degree on whether Participation is a single unidimensional construct, or a large collection of items that all reflect Participation in some way, but do not even represent multiple dimensions. There presumably are key Participation components that no FA instrument would want to omit (work, social relations with family), but the need to, and opportunity for, collecting information on all others is still not known. These and other problems involved in measuring Participation are discussed in greater detail in Dijkers et al. (36).

The presence of an unidimensional continuum underlying functional tasks makes it possible, for those whose interest is more in the patients'/clients'/subjects' status on the construct rather than their performance on each of the individual items, to use computer adaptive testing (CAT) and related techniques to administer very short, targeted sets of items, matched to the individuals' ability (performance) level, that produce the same quantity and quality of information as the more expansive sets of items from which these sets are drawn (37–39). To date, application of CAT to FA has been more demonstration of concept than use in daily clinical and research practice.

### ISSUES IN MEASUREMENT: THE PSYCHOMETRIC CHARACTERISTICS OF FA INSTRUMENTS

Whenever we measure, error creeps into the resulting score, whether it is a small error in measuring simple concrete characteristics (for instance, the area of a room), or a large error in quantifying abstract concepts such as authoritarianism. FA is no exception, and the issue is not so much getting rid of the error (we never will be able to

that completely), but being aware of the amount of error our data contain, and being aware what it means for any conclusions we draw and actions we undertake based on those data. Metrology (the science of measuring) is a major concern in all science disciplines, and the developers and users of FA instruments have mostly relied on the methodologies for instrument development originating in psychology. “Psychometrics” is a very technical and for most clinicians very boring subject, but knowledge of some of the basics is necessary for the fruitful use of FA instruments.

Traditionally, two aspects of the data reflecting the results of measurement have had most emphasis, validity and reliability, but in clinical applications such issues as sensitivity and practicality are increasingly getting attention. In theory, reliability is an aspect of validity, but most people tend to think of them as separate characteristics of instruments (or, more properly, of the data produced by instruments), and the techniques for quantifying validity and reliability are separate. “Validity” refers to the question: is this instrument measuring what it purports to measure? If it is targeting characteristic X, do the numbers reflect X, and not Y, or a little X with a lot of Z? “Reliability” refers to the question: how reproducible is this measurement – if we repeated the measurement operation, with the same or a similar “ruler”, would we get the same result? As illustrated in Figure 16-2, an instrument can be very reliable without being valid. If it is not reliable at all, it by definition is not valid. The goal we are aiming for is instruments that are both valid (they measure what we want to measure) and reliable (they give results that are reproducible).

Over the years, a great many techniques have been developed to quantify validity and reliability, each applicable to different situations. Unfortunately, psychologists and social scientists have fallen into the habit of “inventing” new types of validity and reliability, by naming them after the techniques. However, there is no such thing as test-retest reliability or construct validity. There is only one validity and one reliability of each instrument, which are estimated using different techniques.

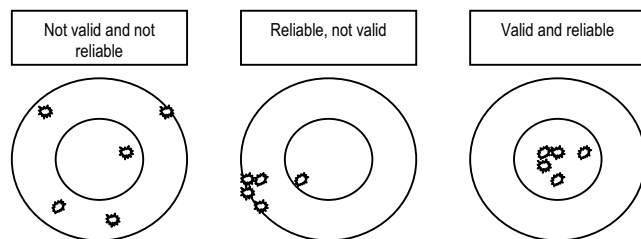


FIGURE 16-2

The relationship of reliability and validity

## Reliability

Estimating the reliability of measures is the easiest to understand. The estimates all are based on some form of repeat measurement. If two clinicians at the same time rate the ability of patient X on the FIM Grooming item, they should come up with the same number – or else one or both are wrong. We can estimate the reliability of the FIM grooming item *as used by these two clinicians* by having the two rate a few hundred patients, and calculate how often they agree – completely, or almost so. A statistical formula such as coefficient kappa (or weighted kappa) can be used to express the result. All these formulas are constructed in such a way that the result, the reliability coefficient, varies between 0.00 (no reliability whatsoever) and 1.00 (perfect reliability). “Interrater reliability” can be estimated based on a few raters to represent all possible raters, so that we can have an idea as to how reliable this one-item instrument is in the hands of the average clinician.

If the same patients are rated by the same clinician twice, we similarly can calculate “intra-rater reliability”, the degree to which she agrees with her earlier ratings. There are two scenarios for this – either the patients’ performance is videotaped, or the rater observes the patients twice. In the latter case, it is of course important that we are sure these patients have not changed in the mean time. In both instances, the clinician should “forget” about her rating the first time around – which is not that difficult if large numbers of ratings are to be made.

Functional status is a fairly broad and abstract entity (a “construct”, in psychometrical parlance), and it is unlikely that a single item such as Grooming can represent the entire construct. Typically, we select multiple indicators (items), and combine them to adequately operationalize the theoretical definition we may have. Use of multiple indicators has another advantage – any random measurement error involved with quantifying any one item is likely offset by the random error in another item. (For that reason, the more items there are in an instrument, the more reliable it will be, *ceteris paribus*, because the chance of random error being eliminated is increased. Any *systematic* error will just remain, however, and practical issues come into play if instruments are too long). Because each item in a FA instrument is a repeat measurement of the construct, like the two raters for Grooming are repeat measures, we can calculate the agreement between items, as yet another estimate of reliability. A number of formulas to estimate “internal consistency reliability” exist, the most frequently used of which is (Cronbach’s) coefficient alpha. “Split-half” and “parallel forms” reliability are related formulas. All of them take values between 0.00 and 1.00.

The minimal level of reliability a measure needs to have depends on the purpose to which the data are to be

put. A minimum of 0.90 for situations where decisions on an individual patient need to be made (discharge Mrs. Jones or extend her stay another week?) is often quoted, while 0.70 or 0.80 is a typical minimum required for group applications, such as in program evaluation and research. Longer instruments tend to be more reliable, but the trend is toward the use of short forms, such as the SF-12 and the CHART-SF rather than long ones, like their parents SF-36 and CHART. With better construction, new short instruments can offer reliability approximating that of older long ones. Another development is computer-adapted testing (CAT), in which only those questions that are targeted to the ability level of the person are being asked (39). For very simple instruments, paper-and-pencil adapted testing is possible (40, 41).

### Validity

Validity cannot be estimated in such a simple way as reliability can, except in one unusual situation: there is an existing instrument that we are certain is perfectly valid. In that case, we can administer the old instrument and the new one to a sample, calculate the correlation between the two scores, and use that correlation as the estimate of the validity of the new measure. The issue of course is: if there is a perfectly good measure, why is there a need to develop a new one? (The importance of having a shorter scale may be the only acceptable reason). Less powerful methods are used in the more common situation: there is no existing measure, or the existing ones are problematic in themselves.

“Face validity” is (in the eyes of most authorities) not a form of validity determination, but an answer to the question: does the instrument “on the face of it” measure what those completing it expect to see – does a measure of X have questions about X that patients recognize as such? Some instruments have no or little face validity, but are perfectly valid – for instance, the Minnesota Multiphasic Personality Inventory (MMPI). In the arena of FA face validity is hardly an issue, because the constructs quantified, or at least the activities that are used as indicators, have a fairly low level of abstraction. The closely related term “content validity” refers to a measure covering the entire construct the developer is targeting, in the eyes of experts. It is generally determined by having the experts draw up lists of necessary content for a measure of X, or checking the content of the draft measure. Of course, this presumes there is a clear description (by the authors) of the concept they would like to operationalize – it makes no sense criticizing a painted portrait on realism if you don’t know the person depicted. There are no standard formulas for calculating this validity aspect.

“Predictive validity” concerns the ability of a measure to predict a future state or event that is inherently linked to the characteristic being measured. A college

entrance examination is said to have predictive validity if it can be used to accurately predict who in four (five, six) years will graduate. A parallel in FA would be the ability of a measure to predict who will be successfully discharged home versus to a nursing home. One problem with predictive validity assessment is the fact that there are no hard and fast rules as to what should be the minimum level of success in predicting. We know that many factors affect successful independent living – the accessibility of the home, family and other support available, the person’s stubbornness and willingness to run risks of falling, etc. Does a FA instrument have adequate predictive validity if predictions based on it are correct 40% of the time? 50%?

“Known group validity” is based on differences in scale scores between two groups that are known to differ in the characteristic the instrument aims to measure. The average score of persons with TBI on a measure of physical functioning should be higher than the average of persons with SCI; in case of a measure of cognitive functioning, the situation should be reversed. If the data do not parallel these expectations, quite likely the instrument is not measuring what we think it is. Alternatively, a lot of systematic error (bias) is reflected in the data. A similar problem as mentioned above occurs with determining known group validity: how much of the variation in the functional status of the overall group should be explained by diagnostic category, TBI vs. SCI? If every person with TBI is known to have a higher physical functioning level than every person with an SCI, things would be easy: the variation explained should be 100%, and everything lower than that would mean less than perfect validity. However, the distributions for functioning ability of the SCI and TBI groups overlap, and the variation explained in a t-test reflects both the difference between group means, the standard deviations around those means, and the random and systematic error in the measure we use. Stating that a good functional measure should explain between 0% and 100% of variance is not very helpful in selecting or developing an instrument.

Lastly, “construct validity” concerns the relationships between the measurement data of a (highly abstract) construct and data for other constructs. Sometimes we have a basis in theory to predict that construct K should be strongly related to (yet not identical with) construct L, and be independent of construct M. (For instance, “ADL ability is related to community integration, but unrelated to political party preference”). If the data brings this out, the operationalization of K should be valid (and similarly the operationalizations of L and M). If the predicted association between K and L is minimal or absent, however, we don’t know if the problem is with the theory, or the operationalization of K, or the measurement of L. And it is an unusual theory that specifies the exact strength of the relationship between K and L, predicated



on perfect measurement of the constructs involved. “Strong” or “very strong” is the best we get, and those are not very good starting points for evaluating the level of validity of the instruments involved.

The above should make clear that the estimation of the validity of instruments always is less straightforward than the quantification of their reliability. Finding high values parallel to e.g. a 0.91 level of test-retest reliability just does not happen; validity coefficients are much lower, because all methods of validity estimation are roundabout. In practice, it is necessary to use all possible methods of estimating validity, and based on multiple findings “patch together” evidence supporting validity – which never will be iron-clad. Finding encouraging levels of the various types of validity distinguished here, in multiple studies, with patterns of correlations that make sense based on expert knowledge, is what typically occurs. Fortunately, in the case of FA, the construct being measured is fairly concrete, and the specialists involved have extensive knowledge of the determinants, correlates, intergroup differences etc. of various aspects of functional status, making the issue of assessing the quality of specific measures less problematic than the preceding list of issues might suggest.

“Ecological validity” does not concern validity proper, but the relevance of assessment data to real-life situations outside the testing situation. For instance, the Wisconsin card-sort test(42) is a measure of executive functioning (the ability to plan, initiate, execute, monitor and correct one’s actions) often used by neuropsychologists to assess persons with TBI. Like all neuropsychological tests, it is administered in a quiet office after the person tested has had a good night’s sleep and is still fresh, etc. How well do the results predict the patient’s ability to make breakfast for her children while testing the middle schooler on history and finishing her own make-up before leaving for work, with the TV competing for attention?(43) Testing executive functioning in situations that resemble the real world would provide data that are more “ecologically valid”, but the standardization of testing might suffer. Standardization of testing has always been a keystone of psychometric methods of assessing reliability and validity of neuropsychological instruments, and of quantifying the abilities of individual patients or clients – they are capacity measures. However, standardized environments tend to be dissimilar from the settings where people perform self-care, communicate, do work and all other things captured under the umbrella of functioning. Testing in a standardized environment almost always means in an optimal environment – and the results tend therefore to be more indicative of capacity than of performance.

### **Sensitivity.**

It is easy to see that if a FA “measure” has just two categories: “able” and “unable”, it lacks sensitivity: it

cannot reflect fine distinctions in ability/performance, and it cannot be used to record minor but clinically significant changes. Sensitivity refers to the ability of an instrument to capture distinctions that are clinically relevant or small enough to be of importance in research, across the full extent of the range of ability of the cases to be measured. When sensitivity is discussed in relation to change, the term responsiveness is frequently used.

Floor effects and ceiling effects are one issue in sensitivity. The first terms refer to the lowest measurable level of performance on an FA instrument being higher than what is the status of the least able person to be measured. All individuals who have ability equal to the lowest measurable level or lower are clumped together and given the corresponding score. Vice versa, a ceiling effect means that the highest measurable level is lower than the level of at least some of the more able patients/clients. It should be noted that very often measures are developed for one population, in which they have no floor or ceiling effects, but then applied to another, in which they do. For instance, the FIM was designed to quantify functional status of rehabilitation inpatients, and any patient who achieves the maximum score on discharge was probably an inappropriate admission. However, a few years after onset of TBI many persons will score at the maximum of the Motor FIM subscale. The FIM was never designed to distinguish between people with minimal deficits that do not affect functioning, other mere mortals, and Superman. Thus, “lack of responsiveness” sometimes is a problem for which the instrument user is responsible, not the instrument developer.

Quantification of responsiveness is not done using formulas resulting in simple coefficients ranging from 0.0 (not responsive at all) to 1.0 (maximum responsiveness possible). All methods are mostly useful for comparing responsiveness of one measure with that of another, allowing one to select the most responsive one. A variety of indices are used, including effect sizes (the mean change between time 1 and time 2 divided by the standard deviation at time 1), the standardized response mean (the mean change between time 1 and time 2, divided by the standard deviation of change scores), receiver operating characteristic (ROC) analysis, and many others. Discussion of these indices is beyond the scope of this chapter; the reader is referred to the extensive literature (44–46). A particular subgroup of these indices involves a rating, typically by the patients themselves, that from time 1 to time 2 they have improved (or deteriorated) a little or a lot, or stayed the same; any FA score changes should correspond to these subjective “transition ratings” (47, 48), or else it lacks responsiveness.

### **Other psychometric characteristics**

Beyond validity, reliability and sensitivity, there are a number of other characteristics of a FA measure that are

relevant to its use in clinical, program and research applications, most of which have to do with practicality:

- **Language:** this is especially relevant to self-administered measures, such as the CIQ (18), but may also be an issue with observational and other measures. Both the reading level and a translation in a language the user is familiar with are of concern
- **Training required:** many observational FA instruments and test-type measures require the user to be trained, and sometimes certified (30), in order to produce reliable data
- **Time and equipment required:** measures that take inordinate time on the part of the subjects or the administrator, or that use special equipment (in some test-type measures such as the Tufts assessment of motor performance (TAMP) (49)) may not be suitable outside research applications

## USES OF FUNCTIONAL ASSESSMENT

The origin of FA (writ small) in medical rehabilitation is in attempts by clinicians to express quantitatively the deficits patients had on admission to rehabilitation, and to monitor progress, or at least determine discharge status, so that there was some “proof” of the effectiveness of treatment, beyond the patient’s simple report that he or she now could do things that were impossible or difficult before admission. The fore-runners of instruments such as the Barthel Index (BI) (25) were simple checklists for recording (lack of) problems with performing self-care and mobility activities (2). From these simple early efforts, measurement instruments of sometimes great sophistication have grown. In addition, the range of applications of these instruments has expanded tremendously, so that we now can describe uses in the care of individual patients, treatment programs as a whole, reimbursement, and research. The type of information needed in these various applications is somewhat different, and even when the basic instrument used is the same (the FIM is the “workhorse” of medical rehabilitation, and is used almost throughout all these types of applications), ideally there would be differences in scoring or other details.

### Uses in care of individual patients

Decisions on admissions to inpatient and outpatient programs are often based on a formal FA, to see if the person has the types and degrees of deficits that the program is qualified and authorized to treat, either in general or for the specific person in question. The “baseline” assessment therefore often is communicated to the third party payor, who may use it to approve program admission and a certain duration or intensity of treatment. The pre-admission

or admission assessment is frequently the basis for a prognosis, which is communicated to the patient and the payor, and ideally underlies goal setting. Many programs use an FA instrument such as the FIM to set goals, either for classes of patients or for individual patients. Software applications have been developed to assist case managers to make such predictions; they are based in large part on a data base that contains the data on many previous patients with the same rehabilitation diagnosis, age, gender and co-morbidities.

Goal setting ideally is more individualized than the limited number of constituent items and/or outcome levels of standard instruments allow. Several methodologies have been developed to allow more or less “customized” selection and quantification of goals, which then are the basis for treatment plan development. Results can be monitored to see if goals are reached (in the time span planned), or need to be modified based on new or initially unknown complicating factors. Goal Attainment Scaling (GAS) is a method originally developed in the mental health arena(50) that has been applied in medical rehabilitation, mostly for research purposes, it seems (51, 52).

In GAS, the client and therapist together set multiple goals, and for each determine the most likely outcome level, as well as two levels of lesser accomplishment, and two of better accomplishment. For instance, for the goal mobility, the target level could be “household walker – can ambulate 50 feet without walker, and without difficulty”. Lower levels could reflect use of supports and/or lesser distance (scored as –1 and –2); higher levels greater distance and/or outdoors mobility (scored as +1 and +2). Each of the several goals (walking; bathing; doing dishes, etc.) is given an importance weight reflecting patient/client valuation. To calculate the overall outcome of treatment, the outcomes for the various goals are summed, after weighting by the importance factors. Thus, the GAS and derivative methods incorporate to some degree the individual valuation of functioning components, but do so only for those actions and activities that display major deficits, rather for all domains of functioning. The end result of the outcomes operationalization reflects success in terms of the goals set, not client functioning in terms of deviation from “normal”. For that reason, these types of instruments may be more useful in clinical applications than in research on the determinants and consequences of functional deficits. Appropriate use of functional measures for goal setting must take into account premorbid function, patient resources (financial assets, family and community support), and known prognostic information. The Canadian Occupational Performance Measure (COPM) (53, 54) uses a methodology very similar to GAS. Ironically, much less is known about the reliability of individualized instruments such as the GAS and COPM than about the measurement qualities of standardized instruments such as the FIM.

Decisions on treatment termination should be based on a number of factors, that include not just functional status (achievement of treatment goal, plateauing) but also family factors, carry over and continuation or generalization of functional skills learned in therapy.

Treatment monitoring using a FA measure is applied in many rehabilitation programs, even if the goals have been set without patient input or without subjective a-priori weighting. Team rounds often exist of the reporting by “most responsible/ knowledgeable therapies” (nursing for bladder; speech for expression, etc.) of the current status of the patient on the numeric items offered by the FA instrument used in the facility. Even before powerful desk-top or hand-held computers existed, various facilities had developed computerized systems for collecting and displaying functional status information – e.g. the Rehabilitation Indicators project (55) and the PECS (33, 34, 56). Even if weekly or less frequent team meetings do not employ formal quantification, the status of the patient with respect to various skills and other aspects of Impairment, Activities and (in outpatient programs) Participation is typically discussed. Almost all rehabilitation programs quantify status on discharge, because that information is needed to document program results, and subsequently is used in program evaluation. While increasingly treatment termination decisions are based on “external” criteria (e.g. a maximal length of stay approved by a third party payor), ideally they are founded on either the accomplishment of goals, or plateauing of the patient in terms of overall functional ability. In both instances, measurement of patient status should be performed using an instrument that has minimal error so that (lack of) change can be reliably determined.

FA information may also be used to communicate about progress and outcomes of treatment with persons who are not part of the team. Patients themselves, their family members, referral sources, and payors have a keen interest in the functional aspects of the patient’s status, especially where it concerns Activities and Participation. One additional use of FA for individual cases is long-term monitoring of a patient’s status. Especially in the case of progressive diseases, this type of information is important to make decisions on new treatments, changes in patient environments, etc. In fact, this use of FA has led to a designation of functional status information as a sixth (after the standard four and pain) vital sign (57).

The foregoing issues suggest that the choice of an appropriate validated FA measure for the individual with TBI depends on a number of factors including: time after injury, rehabilitation setting, and goals of rehabilitation. When clinical improvement is seen, and goals and maybe even the rehabilitation setting (inpatient acute and subacute, etc.) are changed, the measurement tools should be reevaluated. The use of a scale that is insensitive to the improvement that is expected, or not measuring the progress toward an individual’s goal, should be avoided.

### Uses in program administration.

Most rehabilitation programs have as their overall goal something along the lines of: to improve quality of life by reducing impairments and increasing activities and participation level. Program evaluation aims to assess to what degree a program indeed accomplishes what it sets out to do – improve functional status of people with disablement. Basic questions are: do patients change for the better (program effectiveness), and if so, are resources used optimally in accomplishing this (program efficiency).

While change from admission to discharge from a program is common, it is unfortunately not easy to offer proof that the program deserves credit. For instance, a person with TBI may score higher on a post-test than on a pre-test for a number of reasons that have nothing to do with the selection, timing, quality and quantity of services received: natural recovery, improved test-taking ability, and many others (58). All rehabilitation programs face the same problem, and one solution that has been found is to compare outcomes between programs, under the assumption that not *all* change in *all* programs can be explained by causes other than treatment received, and the “excess” change in the best programs is truly the result of interventions. Longitudinal evaluation of a program’s outcomes is facilitated by creation of a minimal data set for all programs that includes demographics, time since injury and measures of injury severity, in addition to specific scales of functioning, selection of which depends on program type and time of follow-up (59). The Uniform Data System (UDS) in which most inpatient rehabilitation facilities in the US participate, as well as some subacute facilities and nursing homes that offer rehabilitation, is one such data aggregator.

Comparisons between programs is fair only, of course, if their inputs (admission status) are the same; it may be much easier to bring an admit FIM score of 50 up to 100 for someone with SCI than for a patient with TBI. Thus, UDS and other aggregators produce reports that compare like with like, in terms of diagnostic group, co-morbidities, age, and other factors considered relevant to chances of program success. The focus tends to be on functional status change over time, as the key indicator of effectiveness. Because the better programs may achieve a certain level of change using much fewer resources than poorly organized ones, length of stay (LOS) is typically used as a gross indicator of resource use. Functional status change per day then is an indicator of program efficiency. (It may be worth repeating here that a number of assumptions, including interval-level measurement of functional status, are made that may not stand up to scrutiny). There are other methods of evaluating a program’s effectiveness, e.g. by evaluating what percentage of the patients did achieve the goals that were set at admission. It is natural that a small percentage of patients

do not progress as well as anticipated, e.g. due to inter-current illness. But if a large percentage fails to make the standardized or individualized functional goals set for them, the program is either selecting the wrong types of patients, or staff and programs are ineffective. Shifts in program admission policies, management or processes may be needed. Unfortunately, routine program evaluation data tend to be insufficient to indicate where exactly the problem is and how it can be fixed; additional studies are needed to obtain that information. However, routine outcome data can and should be communicated to stakeholders, including current and future patients, third party payors, and the local community. The Centers for Medicare and Medicaid Services (CMS) has started to post comparative functional outcomes for nursing homes on its website, and it is to be expected that similar “report cards” including functional FA information will be published in the future for many other facilities that offer rehabilitation of some type.

Choosing appropriate functional measures for the evaluation of a TBI program should be based on what point of the rehabilitation spectrum the program serves. Measures of impaired structure/function would be appropriate for acute inpatient care, with coma scales used for low level patients. Activity measures are most appropriate for acute or subacute inpatient care; Participation measures are needed to assess the effectiveness and efficiency of outpatient services in the community.

The Commission on Accreditation of Rehabilitation Facilities (CARF) (<http://www.carf.org>) is a widely recognized not-for profit accrediting organizations and programs, including TBI programs. It currently offers accreditation in seven categories of brain injury services, including inpatient hospital rehabilitation, residential services, and home and community-based services. Accreditation is based on documenting adherence to standards as well as a surveyors’ evaluation. Depending on the level of care different criteria need to be met. Ensuring patient and family education as well as considering future rehabilitation needs are required components. Outcome measures include appropriate functional assessment during and after treatment. Patient and family satisfaction measures also play an important role.

In addition to program evaluation (which is a CARF-required activity) and accreditation, FA data are used in a variety of activities centering on improving program services quality. Whether they are called outcomes management, continuous quality improvement (CQI), or total quality management (TQM), they all involve considering the organization delivering services as a system, with parts and subsystems that all should be studied continuously to reduce inefficiencies, improve administrative and clinical procedures, and reduce risks and adverse events (3). FA information almost by definition plays a key role in making decisions in programs that deal with individuals with TBI or other disabilities. For instance, an

admission-to-discharge increase in functioning less than a specified minimum could be an indicator threshold violation that triggers an in-depth investigation whether a problem (opportunity to improve processes) exists. FA information could also function as a monitor that is collected routinely to indicate functioning of the program(s) – a vital sign for the organization.

Effective 2002, CMS has, under its Prospective Payment System (PPS), paid inpatient rehabilitation facilities (IRFs), fixed amounts for each patient discharged, rather than reimbursing (adjusted) charges, costs of operations or some other formula used in earlier years and still used by other payors. The fixed amounts are based in part on the functional status of the patient on admission, combined with diagnostic category (stroke, TBI, SCI, etc.) and age category. For functional status a minor variation on the FIM is used, which is embedded in the IRF-Patient Assessment Instrument (IRF-PAI). The combination of diagnosis, IRF-PAI functional status category and age defines a group whose rehabilitation requires unique resources, as acknowledged in the payment amount for each case (60). (This payment is further adjusted for comorbidities (“tiers”), salary levels in the region the facility is located, etc.). The PPS has given facilities financial incentive to hasten if not improve outcomes. Facilities need to ensure they are doing functional assessment accurately to document patient impairment.

The National Committee on Vital and Health Statistics (NCVHS) has recommended capturing and classifying functional status information as part of routine health care transactions, so that administrative databases could be mined and used for a variety of purposes, including monitoring overall population health, health care management, public health planning, predicting costs and financial management, and policy development (61). At the moment, only limited information on functioning is available, mostly through Medicare files, on special populations: those receiving inpatient rehabilitation (IRF-PAI), nursing home residents (Minimum Data Set – MDS), and people receiving home health (Outcome and Assessment Information Set – OASIS). The Subcommittee on Populations of the National Committee on Vital and Health Statistics which investigated these issues suggested that, with modifications, the ICF might be a useful taxonomic system (a “uniform code”) to base such data collection across the continuum of care on. The uniform code would not prescribe *how* to measure functional status, but only specify *what* data elements need to be reported. (In this sense, it would be comparable with e.g. the ICD, which does not specify *how* to diagnose a particular disease, only *what* the disorders of interest are and how they are related to one another). A German group under the guidance of Stucki and associated with the WHO has begun the development of ICF “core sets” – listings of selected Impairments, Activity Limitations and Participation Restrictions

that are of particular relevance to the care and management of a particular diagnostic group (62–64). The ICF allows coding the severity of Impairments, Activity Limitations and Participation Restrictions,(65) but these are very “primitive” methods that do not operationalize measurement. Presumably, productive use of the core sets, especially in applications beyond clinical care, requires a system or systems of functional assessment.

### Uses in research

Program evaluation typically does not address what was done for individual patients (the “black box” aspect of rehabilitation) to explain changes in functional status and link those interventions to outcomes. It also does not systematically address alternative explanations for outcomes, and has no hard evidence for the effectiveness of traditional or innovative treatments. This is where research comes in. Per end June, 2005, Medline contained over 27,000 records classified under “Activities of Daily Living”, which is used to classify papers on ADLs, (chronic) limitations of activity, independent living, and self care. Functional assessment papers are also indexed under other headings – for instance, “geriatric assessment” added another 2,000 plus unduplicated records. Of this total, only a small number addresses clinical application at the level of the individual (presumably less than 5%) and a slightly larger number (maybe 10%) concerns the program level uses of FA measures. Most published research concerns either the development of FA instruments, including assessing reliability, validity, sensitivity, and practicality characteristics, or the use of FA measures to evaluate the effects of rehabilitation, describe the natural course of disablement, assess the financial and social impact of disability, etc.

Because functioning is the central interest of rehabilitation providers and researchers, and their patients/clients, it is to be expected that much of their research uses FA information as either the “independent” (predictor) variable, or the “dependent” (outcome) one, or both. The same holds true with respect to TBI rehabilitation: FA measures, whether specific to individuals to this diagnostic group (CIQ,(18, 66) Disability Rating Scale (DRS),(11)) or generic (FIM) are used in a large percentage of the published research. In this literature one also finds application of very specialized measures (e.g. of functional communication) that will not be covered here. It is worthwhile to remember, though, that before any use is made of its results, this research needs to be assessed in terms of the applicability of the FA instruments selected, and their psychometric qualities.

### SUBJECTIVE VALUATION OF FUNCTIONAL PERFORMANCE

A major criticism of most of the FA measures used in TBI clinical care, program evaluation and research is the fact

that they do not reflect the subjective view of the person involved. “Normal functioning” may be a laudable goal, but not if that functioning detracts from the person’s subjective QOL. For instance, O’Neill et al. found that persons with TBI may do better holding down part-time rather than (normative) full-time jobs. (67). Several studies have shown that measures of participation account for much more of the variance in life satisfaction or well-being measures than do measures of impairment or activity limitations (68–71). Thus, the nature of the fit between functional activities and the person’s values, preferences and abilities needs to be considered and reflected in some way in FA instruments, especially in Participation measures. Corrigan noted that outcomes can be defined from three perspectives: that of the person with TBI, that of the healthcare professionals treating the injury, and that of society (72). The latter two perspective presumably are reflected, to some degree, in the FA measures commonly used. However, the point of view of the insider, the person with TBI, to date has not been investigated with any degree of the attention it deserves.

This case has been made most fervently by Brown and Gordon (5). They argue that in the measurement of social constructs, value judgments are involved, and the values of the insiders (here: persons with TBI) and the outsiders (persons without disability: clinicians, researchers) may be different. Power imbalances occur in measurement whenever the outsider’s values and preferences are incorporated into the means-ends chain leading from interventions to immediate outcomes to ultimate outcomes, with few, if any, mechanisms for tapping into the values and preferences of the insider. Such power imbalances are of concern because the insider’s perspective can vary significantly from that of the outsider.

While most instruments designed to measure aspects of “functioning” have concentrated on the “how independent” and “how much” of acts, actions and roles, a few have explored additional dimensions. GAS and the COPM, mentioned above, are semi-structured approaches by which rehabilitation service recipients formulate individualized goals for therapy and provide perceptions of the adequacy of their performance, their satisfaction with performance, and the importance of each goal to their lives. An importance-weighted sum of outcome serves as the key evaluation measure.

Given their open-ended nature, GAS and COPM goals specified can reflect performance in the domains of Participation and Activity, and even inclusion of Impairment aspects is possible. The choice of goals reflects individual valuation, as does the importance rating. A number of other instruments with standardized content have included importance ratings, such as the MACTAR (73) and many instruments traditionally classified as quality of life measures (74).

Three approaches to measuring participation with attention to both its objective and its subjective

dimensions have been developed. Based on the (draft) CIQ-2, Johnston et al. derived a version in which subjects expressed their opinions and feelings about their participation (75). Each CIQ-2 question about objective aspects of everyday life was supplemented by three questions:

- “How satisfied or dissatisfied are you” with the activity? A 7-point rating scale was offered.
- “Would you like this to change?” Four response categories were offered: no; yes, want more; yes, want less; and yes, want a qualitative change.
- “How important would this change be to you?” Five response categories were offered.

A similar addendum was created by Cicerone et al. for the original CIQ (76). CIQ scores had no correlation with the Quality of Community Integration Questionnaire, and fairly weak correlations with the Satisfaction with Cognitive Functioning, suggesting that satisfaction with the underlying cognitive skills needed for participation not necessarily translates into satisfaction with participation per se, which may be restricted by non-cognitive impairments in the person, or societal barriers.

Similar conclusions were reached in a third study that evaluated a participation instrument we developed that incorporates both objective and subjective elements, the POPS (described below). Brown et al. found that persons with and without TBI rated the importance of the 26 items included in the POPS largely the same (23). At the individual item level, there was a fairly strong relationship between the level of involvement (PO), and desire for change (PS); those individuals (particularly those with TBI) who did little or nothing of an activity almost never wanted to do less, and more often wanted to do more. The PO total score was only weakly correlated with the PS total score (0.22 for the TBI group; 0.16 for the comparison group), again indicating that satisfaction with participation (as reflected in desire to change) is not predicted very well by overall level of participation in those activities that “society” typically declares part of the repertoire of its adult members – the normative view reflected in objective participation instruments.

Subjective measures of the type described have a number of shortcomings, according to critics. First, they typically involve the multiplication of two factors, one an importance rating, the other a satisfaction rating or a desire for change indicator. The critics claim that no measurement model applies to such a procedure, and that therefore the resulting item scores and total scores have no meaning, or at least cannot be considered reliable or valid. The measurement model of classical test theory and that of IRT only recognize simple items each measured on an ordinal scale as input to measurement instruments that operationalize constructs on a (pseudo) interval scale. Another criticism of individualized measures is that if

individuals can determine (by exclusion or even nomination) which particular activities should be included in a measure, and with what weight, the “content” of the construct varies from person to person, and performing averaging and other statistical manipulations makes no sense. However, if the *content* in all instances judged (by the researcher) to be relevant to the construct, there is no problem. Personal construct psychology adherents see this as a strength of the methodology, rather than a weakness.

## SELECTION OF A FUNCTIONAL ASSESSMENT MEASURE

The selection of a FA measure to apply in a clinical, administrative or research situation is not straightforward. A first step always should be determining what one wants to measure: Activity (Limitation) only, or aspects of Impairment and Participation (Restriction) in addition? While there are a few instruments such as the Disability Rating Scale that cover all three domains, they do that often poorly, and using two or three separate instruments may be preferable. A second question is: what aspect of functioning is of interest, capacity or performance, and consequently what type of administration should be selected: testing in a laboratory or other setting, observation, or report by the patient or a proxy. This limits choices, and one’s options might be even more restricted if the population one deals with has particular characteristics that make application of the most common instruments impossible – e.g. intubation. The resources available for administration – a special laboratory, administrator training, time of administrator and subject – typically play a major role. Lastly, metrology characteristics – reliability, validity, sensitivity - should inform the selection, although in some situations the choice of instruments is so limited that one needs to accept a measure with less than stellar characteristics.

The following sections offer thumbnail descriptions of some of the more common FA measures used in TBI rehabilitation and outcomes research, or in similar applications on broader groups. The information offered is necessarily limited. The TBI Model Systems of Care maintain a website, COMBI (Center on Outcome Measurement in Brain Injury) (<http://www.tbims.org/combi/list.html>) that in mid-2005 contained information on 27 instruments commonly used in TBI clinical services and research, including most of the ones listed below. (The ones covered are marked with an asterisk). For each instrument, the following are offered: the actual instrument (subject to copyright restrictions); a syllabus containing administration and scoring instructions; information on administrator training and testing required; a description of the psychometric qualities of the instrument, based on the published literature; and frequently asked questions. The various sections are kept up-to-date by experts, frequently the individual(s)

who created the instrument involved. This resource is highly recommended to anyone needing more information on any of the measures listed below.

## IMPAIRMENT/FUNCTIONAL LIMITATION MEASURES

### Glasgow Coma Scale

The most commonly used and universally accepted TBI impairment instrument is the Glasgow Coma Scale (GCS) (8). The GCS was designed as a brief measure of the depth of coma that can be applied in the acute care setting. Three physical exam parameters are assessed: best visual, verbal, and motor responses. Eye opening is scored 1 to 4, verbal response is scored 1 to 5, and motor response is scored 1 to 6. Total scores, which can range from 3 to 15, typically are stratified into three levels: severe (GCS 3–8), moderate (GCS 9–12), and mild (GCS 13–15) (77). Of the three subscores, the GCS motor score has been found to be the most sensitive to long term outcome (78).

The GCS has been found to be a strong predictor of outcomes including as measured by acute care costs and mortality (79–86). In much research on outcomes of services provided in rehabilitation or the community, the GCS is used as a basic indicator of injury severity. Control for severity by using GCS as a covariate allows a better assessment of the impact of (experimental) treatment. However, it should be realized that the GCS score can be falsely low in the presence of drugs, alcohol, hypoxia or hypotension. Conversely it can be falsely high in the presence of an undetected expanding hematoma. Determining a GCS score may be difficult when a patient is intubated. Meredith published a study validating the accuracy of deriving a verbal score for intubated patients based on eye and motor subscores (87).

## ACTIVITY/ACTIVITY LIMITATION MEASURES

### Barthel Index

The Barthel Index (BI), developed in the fifties by Mahoney and Barthel(25) at one point in time was the major FA instrument in use in rehabilitation in the USA. It was improved upon and supplanted by the FIM, and now mostly has historic significance. However, clinicians and researchers in the United Kingdom, Australia and elsewhere still use the BI and modifications of it. The BI consist of 10 physical functioning items. Feeding, dressing, toilet transfer and stairs are scored on a 3-point scale: can do alone (10 points), can do with help (5), and cannot do at all (0). Grooming and washing/bathing are scored on a two-point scale: can do alone (10 points), can do with help or cannot do at all (0). Bladder control and

bowel control are on a three-point scale: incontinent (0), accidents (5) and unimpaired (10). Chair/bed transfer is also on a three-point scale, but independence gets 15 points, help needed either 10 or 5 (if much help is needed). Lastly, walking 50 yards is on a two-point scale: 15 points if independent, 0 if needs help. If the person cannot walk, wheelchair propulsion is substituted, which has a maximum score of 5 for ability, with or without help. The highest BI score possible is 100, the minimum is 0, and intermediate points are interpreted as percent of maximum. Alternatives and extensions of the BI have been created that add items, make the scoring more sensitive, or otherwise improve on this rather crude but simple instrument (2).

### \*Functional Independence Measure

The Functional Independence Measure or FIM, the dominant FA (writ small) instrument in US and international medical rehabilitation for the last 20 years was created, as part of an effort to develop a uniform system to track rehabilitation data, to improve upon the BI (9). It maintained all the BI items, splitting some, and added tasks reflecting status in the socio-cognitive domain. Initially the FIM for all its components used four-point rating scales, but early on, at the request of clinicians who wanted greater sensitivity, these were replaced by seven-point scales, reflecting a range from total assistance (score 1) to complete independence (score 7). Some recent scholarship suggests that in practice, clinicians cannot reliably distinguish the seven categories, and that a four-category scale may be more useful (88). Extensive manuals have been published to guide raters in how to apply the rating scale in each domain, and how to handle unusual situations, such as: should the motor items be scored with or without the patient's orthosis in place (89).

There are 18 items in the FIM, 13 covering ADLs, bowel/bladder care, and mobility, and 5 reflecting everyday communication and cognition. Some applications calculate a single FIM total score by summing over the 18 items, resulting in a total between 18 (total lack of functional ability) to 126 (normal or almost normal), but a more common algorithm, that has considerable research support(26, 90) uses the 13 motor items to calculate a motor subscale score, and the 5 remaining items to calculate a (socio)cognitive subscale score. More fine-grained subscales have been distinguished in various studies,(91) but for "routine" applications the two-subscale method is satisfactory. Typical administration of the FIM is by observation for inpatient rehabilitation status, and standardized interview for follow-up. However, self-administered versions have been used, and one study even used testing on the entire instrument (92). Testing on individual items is commonly done in research.

Many studies have reported on the internal consistency, test-retest or interrater reliability, validity and other

psychometrics of the FIM, which characteristics have generally been found to be satisfactory, for the motor component more so than for the socio-cognitive one. A quantitative summary of the research up to 1995 is provided by Ottenbacher et al (93). A criticism of the FIM sometimes reported is that it has ceiling effects, either in all diagnostic groups, or in selected ones. However, it should be kept in mind that it was designed for quantifying functional status in acute rehabilitation inpatients; within that population, almost all persons are not at ceiling, although there are exceptions, e.g. for SCI patients on the socio-cognitive scale. Use of the FIM in routine rehabilitation practice follows the rule that if a patient is not observed performing a particular task, that task should be coded 1. For instance, many rehabilitation programs do not ask patients to do a tub transfer on admission, and stairs may never be attempted by some diagnostic groups on admission or discharge. This coding instruction causes “missing information” to coincide with “total assistance”, causing serious distortions when these clinical data are used in research and other applications (60).

A separate version of the FIM has been developed for children, specifically those under 7 years of age, who for developmental reasons do not score maximal on the FIM items, even in the absence of disablement. The WeeFIM has the same 18 items, and the same 7 item categories for each, but the scoring instructions take developmental issues into account (94–96). Among TBI researchers, dissatisfaction with the limited coverage by the FIM of communicative, cognitive, and behavioral disturbances after brain injury lead to the creation of a “FIM-annex”, the \*Functional Assessment Measure (FAM), which offers an additional 12 items in these domains (97). The 30-item FIM+FAM has been subjected to limited testing of psychometric qualities, but appears a satisfactory measure (98).

### **PARTICIPATION/PARTICIPATION RESTRICTION MEASURES**

“Social disability”, “social adjustment”, “social integration”, “community integration” and “handicap” have been the organizing concepts for a number of measures that quantify participation in household and other productive activities, other social role performance, social relationships and similar activities now captured in the rubric “Participation” (36). Of the major “Participation” scales that are found in the (TBI) rehabilitation literature, the Craig Hospital Assessment and Recording Technique (CHART) (10), the Community Integration Questionnaire (CIQ) and the Mayo-Portland Adaptability Inventory (MPAI) (99) are based, to varying degrees, on the handicap concept of the ICDH, the forerunner of the ICF. Three measures based on ICF concepts to date have not

or only on a limited basis been used in published studies with individuals with TBI: Life-H(100); POPS(23) and the Participation Measure for Post-Acute Care (PM-PAC) (101).

#### **\*Craig Handicap Assessment and Reporting Technique (CHART)**

The Craig Handicap Assessment and Reporting Technique was designed to provide a simple, objective measure of the degree to which impairments and disabilities result in handicaps in the years after initial rehabilitation (10). The original CHART, developed in 1992, included domains to assess five of the WHO dimensions of handicap: physical independence, mobility, occupation, social integration, and economic self-sufficiency. Orientation (ability to orient self to one’s surroundings) was added later (102). The revised CHART consists of 32 questions and employs up to seven questions in each of the six domains to quantify the extent to which individuals fulfill various social roles. The items focus on observable criteria and have been worded to minimize ambiguity and promote a consistent interpretation.

Each of the subscales of the CHART has a maximum score of 100 points, which indicates that roles within the domain are fulfilled at a level equivalent to that of the norm: an able-bodied person. High subscale scores indicate less handicap, or higher social and community participation. The CHART was designed to be administered by interview, either in person or by telephone, and takes approximately 15 minutes. Participant-proxy agreement across disability groups has provided evidence in support of the use of proxy data for persons with various types of disabilities. The CHART has been found to be an appropriate measure of handicap that can be used with individuals having a range of physical or cognitive impairments, including individuals with TBI. The instrument has been used for research by the developers,(103–108), and others,(109, 110).

A short form of the CHART (\*CHART-SF) was developed using regression analysis and related statistical methods to select items, followed by rescoring so as to create the same 0–100 ranges as the original CHART displays. The Short Form has 19 items (instead of 32); its metric properties and equivalence to the CHART have not yet been evaluated.

#### **\*Community Integration Questionnaire (CIQ)**

The Community Integration Questionnaire constitutes a measure of rehabilitation outcome after TBI which reflects the values and goals of individuals who have a disability. Willer and his associates developed the CIQ using the following design criteria: brevity; suitable for use in an in-person or telephone interview, conducted with the person with TBI him/herself (preferably), or with a proxy; focus



on behaviors rather than feeling states; no biases resulting from age, gender or socioeconomic status; sensitive to a wide variety of living situations; and value neutral (18, 66, 111). Factor analysis was the basis for selecting from a larger pool of items 15 questions addressing home integration (H), social integration (S), and productive activities (P). These questions focus on involvement in roles and household chores, frequency of activities; one addresses the nature of leisure partners: family, friends with or without TBI. The CIQ has been used extensively in research on individuals with TBI, (67, 76, 108, 109, 112–117) as well as those with other types of acquired brain injury.

Dijkers reviewed the psychometric evidence available for the CIQ, and concluded that there were concerns with respect to reliability and validity; sensitivity and score distributions were problematic, and age and gender biases were prominent (24). He embarked on the development of an updated version (known as CIQ-2), which sought to rectify these problems, while maintaining as much of the old measure as possible. Items were added that broadened the scope of household and social activities, as well as travel and mobility; nature of companions and of the organization where the person works or goes to school were added. The final instrument, consisting of 37 questions, has not yet been published. A preliminary version was used in one published study that incorporated a modification that added a subjective participation component (75).

### **Participation Objective, Participation Subjective (POPS)**

The Participation Objective, Participation Subjective (POPS) measure developed by Brown et al. (23) differs from typical participation instruments in several ways:

- It focuses solely on activities, not on non-activity indicators related to community functioning, e.g., income, whether one's companions are largely disabled or able-bodied. The 26 items range from sexual activity to work, and from paying bills to speaking to strangers.
- It generates two measures: the PO, comprising an "objective" measure of participation, and the PS, comprising a subjective measure.

Subjective assessment (the PS measure) incorporates the preferences of the person by gauging the individual's satisfaction with his/her level of engagement in each activity, weighted by his/her rating of the activity's importance. These product scores are averaged across the 26 items to calculate a total score. In addition, there are five subscores more-or-less paralleling the ICF Activity domains: Domestic life, Interpersonal interactions and relationships, Major

life areas (work, school, etc.), Transportation, and Community, recreational and civic life.

The PO gauges performance in terms of frequency or duration of engagement in activity in real environments, not in terms of degree of impaired functioning. Total score and domain subscores are calculated using an algorithm that takes into account the importance ratings that persons with TBI and non-disabled individuals gave to these items, reflecting "societal" values rather than individual ones. (23).

### **Participation Measure for Post-Acute Care (PM-PAC)**

The Participation Measure for Post-Acute Care (PM-PAC) was designed to measure "participation outcomes of rehabilitation services provided in outpatient or home-care settings" From the literature and existing instruments the developers created or adopted a final set of 33 items in seven domains derived from the ICF: mobility; role functioning; community, social and civic life; domestic life; economic life; interpersonal relationships; and communication. (101). Items were written to "reflect a person's degree of perceived limitation in a particular life situation regardless of cause or means". Most items use a 5-point degree of limitation (not at all to extremely) response scale, but duration and degree of satisfaction are also used. Factor analysis and item response theory models were used to assess the dimensionality of the various subscales; some items needed to be reassigned, but in general the results indicated useful subscales ranging from three to nine items each, in which the "limitation", duration and satisfaction items combined well. Further research, including development of computer adapted testing (CAT) versions, is planned.

## **MEASURES THAT CROSS-CUT ICF DOMAINS**

### **\*Level of Cognitive Function Scale (LCFS)**

The Rancho Los Amigos Level of Cognitive Function Scale (Rancho or LCFS) was designed to describe the typical stages of behavioral recovery following a severe TBI during inpatient rehabilitation (118). The Rancho consists of a single 8-level ordinal item in which each category corresponds to increasingly complex behaviors. (With just a single item, the LCFS differs from the other FA instruments discussed here, and technically is not a "scale"). The simplicity of the scale has brought it into wide use by healthcare providers and payers.

The Rancho has been shown to have a modest degree of validity and reliability (119). Scores on admission to rehabilitation correlate with 24-hour GCS score, length of coma, and duration of posttraumatic amnesia. In addition, the LCFS correlates with the DRS and the FIM and FAM cognitive items (120). Given the

correlations between measures of severity and disability, it is not surprising that the Rancho score on admission to rehabilitation is associated with vocational outcomes (121, 122). When applying the Rancho scale, it should be recognized that it was devised only as a descriptor. Recovery from severe brain injury is not linear. In addition, patients may vary in their Rancho level depending on the time of day and other circumstances. The Rancho is not a particularly sensitive measure of recovery and it should not be used to measure recovery. Patients may skip levels or never go beyond a particular level, despite ongoing progress.

Thus, the Rancho scale is best used as it was initially designed, as a simple descriptive scale. It can offer some advantage in pre-admission screening and communication with healthcare providers/ payers. It can also alert rehabilitation teams to treatment issues they are likely to face.

#### **\*Disability Rating Scale (DRS)**

Rappaport's Disability Rating Scale (DRS) has 8 items that address the three original World Health Organization categories of impairments, disability and handicap (7). The first three items of the DRS (eye opening, communication ability, and motor response) are slight modification of the Glasgow Coma Scale(8) and reflect impairment ratings. Cognitive ability for feeding, toileting, and grooming items reflect level of disability. Handicap is addressed with two items, ability to live independently and employability. Each of the areas of functioning is rated on a scale of 0 to either 3 or 5, with the highest scores representing the higher level of disability. The maximum score is 29 (extreme vegetative state); a person without disability would score zero. The DRS rating must be obtained while the individual is not under the influence of anesthesia, other mind-altering drugs, recent seizure, or recovering from surgical anesthesia.

The DRS is fairly easy to use and can generally be completed in under 5 minutes. It can be scored from direct observation, via clinical interview, or by telephone interview (123). No significant technical training is required to administer the scale. Subjective assessment by clinicians is required for cognitive capacity of self-care, rather than actual observation of self care items. This subjective rating is also used for rating employability and independent living potential. The DRS is more reliable than the Level of Cognitive Functioning Scale (119). It has been used to predict ability to return to employment based on admission and discharge DRS scores (122–124). The DRS has been shown to be an effective scale to track progress across the continuum of clinical services and the course of functional recovery (11, 123).

Many studies have reported good reliability and validity coefficients for the DRS (106, 119, 120, 122, 123, 125–127). Limitations of the DRS include its assessment

of general functioning rather than specific functional changes, its lack of utility in patients with only physical disability, and its poor sensitivity to functional evaluation of mild or very severe impairment (DRS Score >22), where small functional changes may not be reflected in scores (120). Therefore, the DRS is more useful when used in conjunction with more detailed measures of function. For patients with Functional Independent Measure (FIM) scores >25, the FIM may have more sensitivity to changes in rehabilitation than the DRS (128). Subjectivity of rating cognitive capacity may also limit its use in mild or severe injuries. In addition, the DRS falls short in assessing patients with severe apraxia, aphasia, or aphonia as well as those who are "locked in" or have tracheostomies.

#### **\*Mayo-Portland Adaptability Inventory (MPAI)**

The Mayo-Portland Adaptability Inventory (MPAI), developed from a modification of Lezak's Portland Adaptability Inventory, was designed to assist in the clinical evaluation of people during the post-hospital period following TBI, and to assist in the evaluation of rehabilitation programs designed to serve this population. The MPAI can be completed by professional staff, people with TBI and/or their significant others. In the most recent version, MPAI-4, items represent the range of physical, cognitive, emotional, behavioral, and social problems that people may encounter after TBI. MPAI-4 items also provide an assessment of major obstacles to community integration that may result directly from TBI, as well as features of the social and physical environment. The three subscales (Ability, Adjustment, and Participation) have good psychometric properties.

The MPAI-4 and its predecessors have been used in a number of studies initiated by the co-developer and his associates (99, 129–133). Unfortunately, the MPAI has found no use outside this group.

#### **\*Glasgow Outcome Scale (GOS)**

The Glasgow Outcome Scale is a ordinal, single-item instrument used to describe outcome after TBI globally (134). It was commonly used before instruments such as the DRS and GCS were introduced. As a brief outcome scale it has been replaced by the DRS, which offers greater sensitivity to small changes or differences. However, the GOS it is still used occasionally, especially in neurosurgical studies of outcome after TBI. The five categories of the original scale are: dead, vegetative, severely disabled, moderately disabled, and good recovery. The \*Extended Glasgow Outcome Scale (GOS-E), an expanded version of the scale, divides each of the latter three categories in two, creating eight categories and increasing sensitivity of the instrument. A structured interview was introduced

to rectify a second problem of the GOS: fairly low interrater reliability (135). Adequate interrater reliability and content validity have been demonstrated for the GOS-E, and compared to the GOS, the GOS-E has been shown to be more sensitive to change in mild to moderate TBI (136). The validity of the GOS-E is also superior to that of the original measure (137).

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# 17

## Life Expectancy

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### 1. INTRODUCTION

Rehabilitation needs and long-term planning for persons with severe traumatic brain injury (TBI) are covered in depth in other chapters of this volume. Here we consider one important aspect of long-term planning, namely longevity.

It is well known that mortality after severe TBI is exceptionally high in the acute post-injury period. It is perhaps less well known that long term mortality (2 years or more post-injury) is also increased, by comparison with the general population. It follows as a mathematical consequence that the life expectancy is reduced.

There are many studies of short-term survival after TBI. Detailed long-term data, however, and resulting research studies, are relatively sparse. The largest group studied on a long-term basis appears to be in the California Disabilities Database, which includes approximately 4,000 persons with disability secondary to TBI.

In this chapter we review what is known about life expectancy in TBI and present some new findings. Section 2 gives a brief review of key actuarial ideas needed for a discussion of life expectancy. Section 3 discusses the causes of death for which the risk is increased after a serious TBI, and reviews the literature. It is not always recognized that persons with TBI are subject to excess mortality risk from some of these causes. In section 4 we review the literature on life expectancy after TBI, focussing on recent research.

After this we discuss the factors that best predict life expectancy (section 5). It will be seen that, as in other types of chronic disability, the severity of motor dysfunction is the most important predictor of reduction in life expectancy. Later, in sections 6 and 7, we present some new findings on life expectancy and long-term decline in function after TBI. We discuss the effect of quality of care on life expectancy in section 8, the estimation of life expectancy in individual cases in section 9, and offer some conclusions in section 10.

### 2. TERMINOLOGY

It will prove helpful in the later sections to be familiar with the following terms:

- **Survival time:** the actual number of years lived by a given patient or member of a study population. A patient alive at the end of a study period is said to have a **censored** survival time as of that date.
- **Life expectancy:** the **average** survival time in a large group of similar persons. Note that this is not a prediction about any individual's actual survival time, as some survival times will be much longer and others much shorter than average.
- **Median survival time:** the time after which exactly half of a large group of persons are still alive. If all



the survival times are known (uncensored) and ordered from smallest to largest, the median is the middle value.

- **Exposure time:** the total number of person-years lived by all the members of a study population during the study period.
- **Mortality probability:** The chance of dying in a given period (e.g., a year). Like all probabilities, this number is between 0 and 1 inclusive.
- **Mortality rate:** The number of deaths in a study population divided by the number of person-years of exposure time. This is always larger than the mortality probability over the same period. Except in very high-risk populations, where the mortality rate could be greater than 1.0, however, the difference between the two is small.
- **Standardized mortality ratio (SMR):** the ratio of the observed number of deaths in a study population to the expected number, where the latter is what would arise from a suitably chosen reference group (often the age- and sex-matched general population in a given country). For example, an SMR of 2 means that the study population has twice the death rate of the reference group, after adjustment for age and sex differences. For further discussion, see Kahn & Sempos (1).
- **Relative risk (RR):** the ratio of the mortality rate in a study population to the mortality rate in the reference population. Unlike the SMR, the expected number is not standardized to the age and sex distribution in the reference population. The RR is often termed the **mortality ratio (MR)** in the actuarial literature.
- **Excess death rate (EDR):** the difference between the death rate in a study population and that in the reference population.
- **Life table:** a standard table summarizing mortality information about a group. Life tables are constructed for entire populations (2–6) or for suitably large subgroups (7–11). The table derives entirely from a set of age-specific mortality rates, and gives the life expectancy at every age. The median survival time can be easily computed from table entries (12, 13).

### 3. CAUSES OF DEATH AFTER TBI

It is clear from the published literature that there is an increase in long-term mortality in persons who have suffered a severe TBI. The published studies are, however, not entirely consistent on which causes of death account for the excess.

In the very short term, the primary cause of death is the brain damage itself. One of the largest studies was that of Sekulovic and Ceramilac (14), who summarized

autopsies of 499 deaths occurring within 30 days of traumatic brain injury. They found that 78% of the deaths were due to injury to brain stem, brain edema, or brain compression. Of the remainder, the most frequent cause was pneumonia.

The definition of “longer term” varies among the studies. For example, Baguley et al. (15) considered patients who had been released from the hospital into rehabilitation facilities, while Shavelle et al. (16) considered one year or longer post injury.

The published studies make clear that, even in the long-term, death rates from many different causes are elevated for persons with TBI by comparison with the general population. These causes are considered below.

- **Epilepsy.** We refer here to post-traumatic epilepsy, rather than post-traumatic seizures. Post-traumatic epilepsy refers to recurrent long-term episodes often observed in persons with TBI, while the term post-traumatic seizures is generally applied to events in the first post-injury week.

The classic studies of World War II veterans with TBI first documented the increased mortality risk from post-traumatic epilepsy (17). Later studies similarly addressed World War I veterans and reported the same finding (18, 19). This was confirmed in Roberts’ long-term follow-up of patients in England during the 1960’s and 70’s (20, 21) and in Rish et al.’s study of veterans from the Vietnam war (22). More recently Shavelle et al., in their study of Californians with long-term mental disabilities from TBI, estimated a standardized mortality ratio (SMR) for seizures of 24 by comparison to the general population (16). Even patients with less severe disabilities were subject to an increased risk.

The literature shows that epilepsy is more common in penetrating head injuries, such as gunshot wounds, than in non-penetrating injuries (23–27). One might expect that the severity of epilepsy would be greater, and therefore the mortality risk higher, for those with penetrating injuries. There does not appear to be any available evidence on this, however.

- **Suicide.** Roberts (20) found an increased suicide rate (SMR = 3) over the long term. A similar finding, and one documented in greater detail, was reported by Teasdale & Engberg (27). The latter authors, in their large study of Danish patients with TBI, found a suicide rate approximately four times that of the general population. They point out that persons with certain psychiatric conditions may be prone both to have accidents causing TBI and to commit suicide, though it seems unlikely that this could explain most of the association. A recent study by Pentland et al. (150) also found an increased proportion (1.3% of all deaths) due to suicide.

No increase in the suicide rate was observed by Walker and Blumer (28) or Shavelle et al. (16).

- **Respiratory infections and pneumonia.** Many studies document the increased risk of death due to these causes in patients with severe TBI. This is especially marked in persons who have become nonambulatory. Shavelle et al. (16) reported an approximately ten-fold increase in the mortality rate from respiratory causes, and Pentland et al. (150; Figure 2) found it to be the leading cause of death in this population after cardiac diseases. It appears that it is primarily the immobility, not the brain injury per se, that increases the risk; for example, a similar finding is reported in patients immobilized by spinal cord injury (29, 30).
- **Meningitis** was reported as an increased risk by Roberts (20), but not by other researchers (15, 16, 22).
- **Diseases of the circulatory system** are the leading cause of death in Western countries, and in the long-term the risk of death appears to be even higher in persons with severe TBI. Shavelle et al. (16) reported an approximately tripled mortality rate from these causes, by comparison with the general population, which by itself indicates a substantial reduction in life expectancy. Not surprisingly, the increase was largest among patients who had become nonambulatory. Weiss et al. (19) also found a long-term increase in the death rate from diseases of the circulatory system.

There are at least two mechanisms that could contribute to the increase in circulatory disease, and related deaths. First, persons confined to a wheelchair often take little exercise, and this alone increases the long-term risk of circulatory disease (31–35). Secondly, paraplegia appears to increase the risk of embolisms that travel from the lower body to the brain or lungs, and are often fatal. We are not aware of any studies that quantify these effects after TBI specifically, but a similar pattern of increased mortality has been observed in persons immobilized from spinal cord injury (29, 30) or cerebral palsy (59).

As with others who are immobile, persons suffering a TBI have an increased incidence of morbidity due to deep vein thrombosis, pressure sores, sepsis and urinary tract infections (36–48). However, there do not appear to be any studies documenting increased long-term mortality due to these causes. Of the 135 deaths described in Table 17-1 below, only one was due to any of the above (urinary sepsis).

Walker et al. (18) suggested that an injured brain makes the entire body more vulnerable to the stresses of aging. Lewin et al. (21, p. 1535) doubted Walker's hypothesis, pointing out that in their own study only a small number of causes of death appeared to be elevated

**TABLE 17-1**  
*Causes of Death for Persons Injured at Ages 10 or Older Who Died 5 or More Years Later*

CAUSE OF DEATH (ICD-9 CODES)	NUMBER	%
Cancer (140–239)	9	7
Seizures (345, 436, 780.3)	14	10
Circulatory (390–459, except 436)	26	19
Respiratory (460–519)	15	11
Digestive (520–579)	6	4
Urinary/kidney (580–599)	4	3
Choking/suffocation (910–915)	3	2
Other external (800+, except 910–915)	13	10
All other causes, including missing	45	33
Total	135	100

in their TBI population. As noted earlier, however, the much larger study of Shavelle et al. (16) found increased mortality from most major causes other than cancer, which may support the view of Walker et al.

Table 17-1 shows causes of death for persons injured at ages 10 or older, who died 5 or more years after injury. The data are from the California Disabilities Database over the period 1988 to 1999 (49).

Excluding the “All other causes” category, the largest category was circulatory diseases. The comparatively small proportion of cancer deaths reflects the increased number of premature deaths to other causes; for example, there were more deaths due to respiratory diseases and seizures than to cancer.

#### 4. RECENT LITERATURE ON LIFE EXPECTANCY

There is an abundant literature on short-term survival after TBI. The focus here is on the major recent studies on long-term survival. For a detailed history of studies prior to 1979 see Roberts (20, chapter 4).

- Walker and Erculei (17, 50) studied 364 World War II head-injured men from injury to 15 years later. The authors found a death rate 3 to 4 times greater than expected. They analyzed the frequency and severity of seizures, noting that men with post-traumatic seizures did not, on average, survive as long as those without seizures.
- Walker et al. (18) analyzed survival data through 1965 on 574 German World War I head-injured men. This ambitious study included a contemporary

control series of 581 unwounded veterans receiving meritorious medals. They constructed life tables and found a roughly 4-year reduction in life expectancy in the TBI group, with a larger reduction for those with epilepsy.

- Roberts (20) followed 469 patients who were amnesic or unconscious for a week or longer after a severe head injury. His analysis concentrated on the 366 who were discharged alive from hospital. He found that the chance of dying in the first 20 years after injury was elevated only in those injured at ages 5 to 25, and concluded that the effect of TBI on life expectancy was a 5-year reduction (20, p.146).

It appears from Roberts' Table 5.3 that some 80–90% of these persons could walk unassisted. If so, his conclusion would not apply to the most severely injured patients who were wheelchair-dependent or even bedridden. It has sometimes been inferred, incorrectly, that the Roberts' estimated 5-year reduction applied regardless of the severity of disabilities. Roberts himself evidently did not hold this view, as he reported that persons with the most extreme disabilities rarely survived ten years (20, p.142).

- Rish, Dillon and Weiss (22) studied 1127 Vietnam veterans who survived one week or longer after a penetrating head injury. The all-cause SMR over the 15-year study period exceeded 4 during years 1–3, ranged from 2 to 4 during years 4–11 and 13 post-injury, and was (probably because of the small sample size) less than 1 for years 12, 14 and 15. The authors concluded that the study population may have "approached the norm."
- Corkin, Sullivan and Carr (51) studied 190 World War II veterans with penetrating head injuries and a matched set of 106 with peripheral nerve injuries. They reported that head injury coupled with epilepsy reduced life expectancy compared to the control group, but that head injury alone did not.
- Walker and Blumer (28) studied 244 World War II head-injured men with post-traumatic epilepsy and found a death rate several times higher than in the general population.
- Strauss, Shavelle and Anderson (52) studied 946 children and adolescents aged 5 to 21 who suffered a TBI, following the subjects for up to 9 years. They constructed life tables stratified by a crude mobility scale (none, poor, fair/good). The resulting reductions in life expectancy, compared with the general population, ranged from very large (40 years) in persons with the most severe disabilities to quite small (2 years) in those who retained good mobility.
- Baguley et al. (15) studied 476 patients injured from 1986 to 1996. During the average follow up time of 5 years there were 27 deaths, compared to 6.7 expected, giving an SMR of 4.0. The difference was

highly statistically significant, again demonstrating that life expectancy after TBI cannot be considered normal.

- Shavelle and Strauss (53) computed excess death rates for persons with TBI, beginning two years after injury. The population studied was the largest in the literature, with 2629 subjects and 268 deaths in the 1988 to 1997 study period. As in their previous studies, these authors found that excess death rates were relatively small for ambulatory persons, but much larger for those who had become nonambulatory.
- Brown et al. (151) followed up on 1,448 persons with TBI, of whom 164 (11%) were described as having moderate to severe injuries. They found that persons with mild TBI exhibited a small but statistically significant reduction in long-term survival. For those with moderate or severe TBI, long-term survival of those who survived the first six months was similar to those with mild TBI. A difficulty in interpreting this last finding is that the "moderate to severe" range presumably contained a mixture of persons with extremely severe disabilities (for whom the life expectancy is without question markedly decreased) and persons with much less severe disabilities. The overall effect therefore depends on the relative proportions.
- Harrison-Felix et al. (152) followed 2178 persons with TBI who completed inpatient rehabilitation in one of 15 National Institute on Disability and Rehabilitation Research-funded TBI Model Systems of Care. They estimated an average reduction in life expectancy of 7 years. In a follow up publication jointly written with the present authors (153), they indicated a general approach to estimating the life expectancy of an individual of a given age, sex, and score on the Disability Rating Scale. For example, according to the Model Systems data the life expectancy of a young adult with an "extremely severe" disability is 50% of normal. This again indicates how life expectancy after TBI varies greatly according to the severity of the injury.

While some of the studies — most notably, those of subjects without epilepsy — did not report a substantial reduction in life expectancy in some groups, this may be because persons in those groups were less severely disabled. There can be no question that mortality is markedly increased among the most severely disabled patients, a pattern well documented also in cerebral palsy (54–65) and spinal cord injury (19, 30, 66–70). In discussions of life expectancy of persons with TBI, therefore, it is important to consider the severity of disability.

Persons with more severe injuries are much more likely now than in the past to survive the early high-risk period (22). Other things being equal, it may therefore be

that the more recent studies have a higher proportion of severely disabled persons. This would have obvious implications for the comparison of older and newer studies.

## 5. FACTORS RELATED TO SURVIVAL

The best predictors for survival in the *short* term are clinical measures such as the patient's Glasgow coma scale and duration of post-traumatic amnesia. The concern in this chapter, however, is with factors predictive of long-term survival.

For persons with TBI as well as in the general population, age is of course the most obvious determinant of life expectancy. Apart from age, the key factor is the severity of disability, especially motor dysfunction. This can be measured by simple functional items such as the patient's ability to walk, use hands, and self-feed. Other factors (such as preserved cognitive function or epilepsy) have a relatively small effect once motor function has been accounted for.

We now consider the factors that have been considered significant for life expectancy, citing the available evidence.

- **Age.** The increase in mortality of persons with TBI with age has been documented in many studies (52, 53, 71–74).
- **Sex.** In the general population, mortality of males at most ages is appreciably higher than that of females (2–6). For example, in the U.S. general population males age 30 to 60 have about twice the risk of death as females (2). Similar sex-differences have also been observed in persons with TBI (35). As would be expected, the difference is most marked in persons with milder disabilities and all but disappears at the most severe end of the spectrum. For example, no sex difference was found in the survival of persons in the permanent vegetative state (75).
- **Time since injury** is certainly an important factor in the short-term. The mortality risk declines steadily during the first two years after injury as the patient's condition stabilizes. In the much longer term, however, there is no clear evidence of a trend, once severity of disability is taken into account. For example, mortality rates of persons 5 years post-injury do not seem markedly higher than otherwise comparable persons 10 years post-injury (49).

Because mortality after severe TBI is so high shortly after injury, it has sometimes been suggested that individuals vary greatly in their "toughness": only the tough survive the initial post-acute period, and these individuals are likely to survive much longer. No doubt individuals do vary to some extent in their abilities to survive major trauma. A more

plausible explanation, however, is the well-known "healthy survivor" effect: persons with the most severe injuries die first, and the remainder have better survival because their injuries are, on average, less severe. This explanation is consistent with our finding that after the first few years, mortality rates are fairly constant over time once mobility and other factors are taken into account.

- **Mobility** is the most powerful predictor of long-term survival after TBI. Using the extensive California Disabilities Database, Strauss, Shavelle and Anderson (52) found a large difference in survival based on an overall mobility scale (none, poor, fair/good). The risk of death for persons with no mobility was approximately four times higher than those with fair or good mobility, even after adjustment for several other factors.

Shavelle and Strauss (53) subsequently computed age-specific mortality rates for three levels of ambulation (walks well alone; walks with support or unsteadily alone; does not walk). The age-specific mortality risks relative to the general population ranged from as low as 1.3 to as high as 17. Additional research indicates that, as would be expected, still more precise discrimination can be made based on more refined measures of motor function (49). Similarly, Baguley et al. (15) found that Functional Assessment Measure score was associated with survival.

- **Feeding ability.** Strauss, Shavelle and Anderson (52) found a sharp contrast in survival between four groups of persons: those requiring a feeding tube (RR = 6.6 compared to the best group), those fed orally by others (RR = 2.9), those who could finger feed (RR = 2.1), and those who could use utensils (the best group, with RR = 1 by convention). The inability to self-feed is an indirect measure of neurological compromise. It seems likely it is this compromise that causes the increased mortality, and the inability to self-feed is primarily a marker for it.
- **Need for ventilator support, oxygen, and/or frequent suctioning; history of respiratory problems.** We recently investigated the effect of these factors (49). Each was much more common in persons who could not walk and who required a feeding tube than in persons who were higher-functioning. In the former group, the univariate effect — that is, when no adjustment for mobility, etc. was made — was statistically significant and large: the relative risks for the factors ranged from 2 to 6. However, once age, sex, mobility and feeding were accounted for the (multivariate) relative risk was less than 1.2 for each factor.
- **Deficits in cognitive function and ability to communicate** are strongly correlated with severity of motor dysfunction. Although cognitive and communicative

functions are strong univariate predictors of mortality, their effects are modest when motor function is taken into account (49, 52). The same finding has been documented in persons with cerebral palsy (61, 62).

- **Epilepsy.** Many authors have found that epilepsy was strongly associated with reduced survival (17, 19, 50, 51). However, as others have suggested, this was likely because the presence of post-traumatic epilepsy is highly correlated with the extent of brain damage (17, 22). That is, epilepsy served as a marker for injury severity. Nevertheless, epilepsy is an independent risk factor for increased mortality. We recently confirmed this, and additionally found that in those who cannot walk, the relative risk of death for persons with generalized tonic-clonic seizures is 1.2 compared to others (49). In a separate study of people with minimal physical disabilities, Strauss et al. (76) similarly documented the increased mortality associated with recent seizures.
- **Calendar year.** The question is whether survival rates have improved over the years for a patient of given age and severity of disability. This would be termed a *secular trend*. The available data does not reveal any evidence of such a trend in recent (1980+) years (15, 49, 52). This may seem paradoxical because (i) as noted in other chapters of this volume, advances in rehabilitation have improved functional outcome after TBI, and (ii) as documented above, functional outcome, specifically mobility and feeding skills, are key factors associated with life expectancy. Thus it may well be that among patients with similar *initial* injuries, survival now is better than in previous decades because functional outcome is better. The cited research (15, 49, 52), however, looked at a different issue: comparison of survival now and in the past of patients who have the same *functional outcome*.

Several other factors should be mentioned as possible predictors of survival:

- **Poor education.** This factor was noted by Corkin, Sullivan and Carr (51). They suggest many reasons for the increased risk of death, including subsequent occupation and access to health care. To our knowledge other researchers have neither confirmed nor disproved this.
- **Depth of brain injury.** Weiss et al. (19) found that, as expected, the survival was poorer in persons with deeper (greater than 3 cm) brain injuries, although the difference was not statistically significant.
- **Penetrating versus closed head injuries.** Baguley et al. (15), in comparing the literature, concluded that there was no evidence of a difference. After controlling for

functional abilities we too could find no difference, though the power of this comparison was low (49). Zafonte et al. (77) also found no difference in functional outcome at one year post-injury. On a related point, we found no difference in survival (49) between those who suffered skull fractures (ICD-9 codes 800–804) versus intracranial injuries (850–854). Finally, it may be that the effect of epilepsy is different in penetrating versus closed injuries, though evidence on this does not appear to be available.

- **Duration of unconsciousness.** Neither Shavelle and coworkers (49, 52) nor Weiss et al. (19) found this to be a significant factor. Lyle et al. (78) found that duration of coma was associated with both recovery and survival to 2 years, but it is not clear if this result would hold true if attention was restricted to those alive at 1 year post-injury, and if the functional outcome — e.g., mobility — was accounted for.
- **Glasgow coma scale (GCS) and the duration of post-traumatic amnesia (PTA).** Again, these factors are measures of the severity of the injury, are highly correlated with short-term survival, and therefore have a relationship to subsequent longevity. We are not aware of any evidence, however, that either of these factors is associated with subsequent long-term survival given the functional outcome one year post injury.
- **Maladaptive behaviors** — such as drug use, other substance abuse, suicide attempts, assault, aggression, self-injurious behavior, and lack of safety awareness — are much more common in those who have suffered a TBI or other central nervous system trauma than in the general population. For example, several studies report an association between CNS trauma and criminal behavior, especially violent crime (79–81). Such behaviour is also more frequent in persons with TBI than in others with comparable levels of functioning whose disabilities are due to cerebral palsy, autism, and other conditions (32).

These behaviors, with the exception of safety awareness, were *positive* factors for life expectancy when considered in isolation (49). That is, for example, persons who abused drugs had a *lower* mortality rate (and thus higher life expectancy) than those who did not. This is not surprising as those who could exhibit the behaviors were much less severely disabled, on average, than those who could not. In fact, these factors had a small *negative* effect on survival once functional abilities were taken into account (49).

Maladaptive behaviors in general have all been shown to be associated with increased mortality. For a review of the epidemiological data, see Harris & Barraclough (82). As these authors show, a major component of the increase is deaths due to unnatural causes, including accidents, suicide and homicide.

It may be that the reduced life expectancy of relatively high-functioning persons with TBI in part reflects an increased rate of unnatural deaths associated with behavioral problems.

- **APOE 4.** It is also possible that the APOE 4 allele plays a role. As noted by Baguley et al. (15) in citing Teasdale et al. (83) and Friedman et al. (84), patients with the APOE 4 allele are more likely to suffer unfavorable outcome after severe traumatic brain injury. Recent research (85, 86) on this issue has found that the presence of the APOE 4 allele is associated with poorer memory performance and rehabilitation outcome after TBI. Research by Liberman et al. (87), however, did not show a consistent influence of APOE genotype on outcome. We are not aware of any data on the independent effect of this allele on long-term survival.
- **Quality of care** is addressed separately in section 8.
- **Other factors relevant to life expectancy in the general population** are also relevant for persons with

TBI. These include pre-injury health status and history of smoking, alcohol and drug abuse, obesity, etc. Scientific literature on the effect of most of these factors is available.

- There are **factors uncommon in the general population** that can affect the mortality risk of persons with TBI. Examples are difficulties with chewing and swallowing, contractures, pressure sores (for persons with limited mobility), bowel and bladder dysfunction, frequency of infections, and psychological factors (attitude to the disability, depression, aggressive behavior, etc.). For many of these factors, published studies of the effect on mortality are not available.

## 6. NEW ESTIMATES OF LIFE EXPECTANCY IN TBI

Tables 17-2 and 17-3 show our most recent findings (49). These represent a refinement of the data presented in our

**TABLE 17-2**  
*Female Life Expectancy by Age and Severity of Disability*

AGE	PVS <sup>a</sup>	CANNOT WALK		SOME WALKING ABILITY <sup>d</sup>	WALKS WELL ALONE <sup>e</sup>	GENERAL POPULATION
		FED BY OTHERS <sup>b</sup>	SELF FEEDS <sup>c</sup>			
10	12	27	46	55	61	70.0
20	11	26	40	48	54	60.2
30	10	22	33	41	46	50.5
40	9	16	26	31	36	41.0
50	7	11	19	23	27	31.7

<sup>a</sup>Permanent vegetative state: No purposeful motor or cognitive function. Requires a feeding tube.

<sup>b</sup>Does not feed self, must be fed completely (either orally or by a feeding tube).

<sup>c</sup>Can feed self with fingers or utensils, with assistance and/or spillage.

<sup>d</sup>Walks with support, or unsteadily alone at least 10 feet but does not balance well.

<sup>e</sup>Walks well alone for at least 20 feet, and balances well.

**TABLE 17-3**  
*Male Life Expectancy by Age and Severity of Disability*

AGE	PVS <sup>a</sup>	CANNOT WALK		SOME WALKING ABILITY <sup>d</sup>	WALKS WELL ALONE <sup>e</sup>	GENERAL POPULATION
		FED BY OTHERS <sup>b</sup>	SELF FEEDS <sup>c</sup>			
10	12	27	46	50	56	64.3
20	11	26	40	44	49	54.7
30	10	22	33	37	41	45.4
40	9	16	26	28	32	36.2
50	7	11	19	20	23	27.4

<sup>a</sup>Permanent vegetative state: No purposeful motor or cognitive function. Requires a feeding tube.

<sup>b</sup>Does not feed self, must be fed completely (either orally or by a feeding tube).

<sup>c</sup>Can feed self with fingers or utensils, with assistance and/or spillage.

<sup>d</sup>Walks with support, or unsteadily alone at least 10 feet but does not balance well.

<sup>e</sup>Walks well alone for at least 20 feet, and balances well.

earlier publications, and take account of age, sex, and walking and feeding ability. For comparison, life expectancies in the permanent vegetative state (PVS) and the U.S. general population are also shown. As can be seen, the remaining life expectancy decreases both with age and with severity of injury.

At the most severe end of the disability spectrum, the permanent vegetative state (PVS), the life expectancy is at most 12 years, and no significant differences were found between the sexes. The PVS analyses are specific to persons with acquired injuries, including TBI and near-drowning, and who will require gastrostomy feeding for life. The corresponding figures (not shown) for persons with congenital conditions, degenerative diseases, or who require a ventilator are lower still.

Persons in the minimally conscious state (MCS) – a group that has received recent attention in the clinical literature (88–90) – have slightly higher cognitive function than those in the PVS. A study of infants who were immobile and in the MCS (“IMCS”) found that their survival was only slightly better than those in the PVS (91). Thus, once again, mobility is seen to be a more important predictor of survival than cognitive function. A subsequent analysis of 2,534 children and adults who were in the IMCS gave the same finding (49).

The nonambulatory group covers a wide range of functional abilities. At the low end of the range are persons in the vegetative state, and those who are immobile and require gastrostomy feeding. At the high end are persons who feed themselves, and have reasonable self care skills, even though they cannot walk. Tables 17-2 and 17-3 include a simple stratification on the basis of self-feeding, an important predictor of life expectancy. Further distinctions can of course usefully be made.

It should be pointed out that there are persons whose residual TBI is so mild that they do not require services (e.g., occupational and physical therapy) on an ongoing basis. These persons would not be in the California data base, and their life expectancies may be higher than any group described above. In the best case, where the effects of the TBI are minimal, the life expectancy is of course essentially normal, or even better than normal (if, for example, the person was a nonsmoker, took regular exercise, maintained a good weight, etc.).

Persons in the highest functioning group of the table — those who can walk well alone and balance well — nevertheless have disabilities severe enough to require ongoing services. The aggregate life expectancy is reduced by 4 to 9 years compared to the general population. As expected, the difference is smallest for the oldest persons. Note that there is no sex difference in life expectancy in the most severely disabled category, but a substantial difference among the higher functioning groups.

The TBI figures in Tables 17-2 and 17-3 do not take account of whether the person needs a feeding tube. This

need is uncommon in the higher-functioning groups, but about half of the persons over age 10 who cannot walk and cannot feed themselves do require a feeding tube, and their life expectancy is lower. Also not considered are specific fine and gross motor skills and cognitive ability, all of which affect life expectancy to some extent.

*Technical Note* The scientific methods underlying the study of life expectancy are well-documented in the actuarial, epidemiological and statistical literature; see, for example, Singer (91), Kahn and Sempos (1), Collett (92), Schoen (93) and Anderson (12). Full details on the specific methods used to compute the results in Tables 17-2 and 17-3 are described elsewhere (75, 94, 95). A brief summary follows:

- The analyses were based on data from 1,723 persons at all ages (PVS) and 3,598 persons over age 10 (TBI).
- A data set of person-months was constructed — PVS: 56,229 person-months; TBI: 285,424 person-months. Each person-month was associated with the subject’s age, severity of disability, etc., and an indicator variable for whether the person died in that month.
- Logistic regression was used to compute the annual mortality rates. The following factors were used:
  - **PVS analyses:** age, time since injury, etiology, and need for feeding tube.
  - **TBI analyses:** age, sex, time since injury, and the walking and feeding categories listed in the table.
- The PVS analyses provided mortality rates for all ages. The TBI analyses provided rates at the starting ages and a model was used to compute rates at subsequent ages. A life table or survival curve was then constructed, with the life expectancy obtained directly in the former case, and as the area beneath the curve in the latter.

## 7. LONG-TERM DECLINE IN FUNCTION

In the short term, patients with TBI often regain some functioning in the first year post-injury (96–98), but the rate of recovery slows thereafter (28, 99, 100). An exception is the elderly, who have a low rate of recovery even in the first year (101–104).

It appears that, over the long term, patients with TBI will lose functional abilities faster than those in the general population:

- Lewin et al. (21) reported progressive intellectual deterioration in their patients, more so than would occur in the general population.
- A relevant comparison may be with persons who have suffered repeated (“chronic”) TBI, as contrasted to acute TBI. Chronic TBI can result from boxing

(105, 106) and possibly from “heading the ball” in soccer (107–110). It is an often-progressive neurological condition with many of the same pathological characteristics as Alzheimer’s disease (110–112).

We investigated this issue of long-term decline in our TBI database, concentrating on one important functional measure: ambulation.

Figure 17-1 shows the long-term prognosis for a group of 100% who initially could walk with support (crutches, braces, etc.) two years post-injury. Of these, roughly 15% died within the next 8 years, 20% lost the ability to walk, 55% did not change, and 10% could walk well alone. That is, of those still alive twice as many declined in functioning as improved.

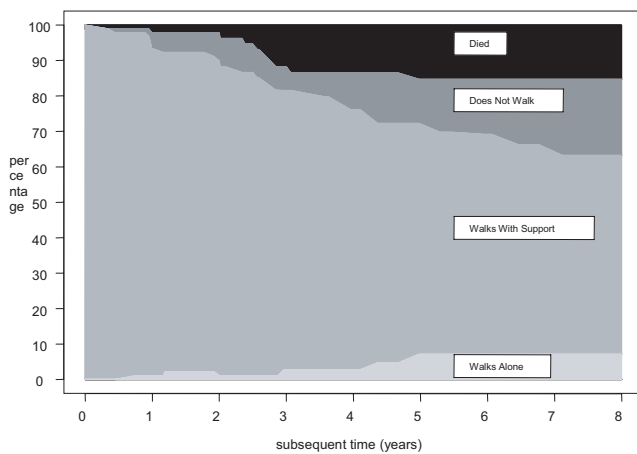


FIGURE 17-1

Long-term change in ambulation for adults aged 40 and over

*Technical Note* The curves for the cohort, including the survival curve, were computed using the Aalen-Johansen estimator (113). This statistical method was developed as an extension of the usual Kaplan-Meier (114) estimator to address the case of multiple live states (115). Day (116) showed that, in statistical parlance, the estimator is consistent and more efficient than the extended Kaplan-Meier estimator proposed by Strauss and Shavelle (117). The latter has previously been used to produce similar diagrams involving improvement or decline in function of persons with developmental disabilities (62, 118).

## 8. QUALITY OF CARE AND LIFE EXPECTANCY

Quality of care is a rather vague term that is frequently raised in discussions of life expectancy. It seems to cover a variety of issues, including:

- The expertise of the caregivers, ranging from highly qualified professionals to relatively unskilled (and

low paid) staff. A complicating factor is that caregivers are often family members, who generally do not have formal qualifications but in some cases become highly skilled carers.

- The accessibility of physicians and emergency services.
- The quantity of care and equipment provided, which is often a reflection of the funds available.

The effect of quality of care on life expectancy surely depends on what is being compared. If, for example, it is good care versus negligent or even deliberately substandard care, the difference in life expectancy will doubtless be large. This comparison, however, is generally not of interest. The most relevant comparison is between:

- The normal, standard care available in most Western societies, and
- The care expected given that the patient has a carefully prepared and well-funded life care plan.

It might be argued that the care embodied in (b) represents the best case in practice, as one cannot forecast exactly what care the patient will receive, or will choose to receive, in the coming decades.

The issue is evidently a complex one and we do not attempt to draw any definitive conclusions. Nevertheless, these observations may be helpful:

- Some states or countries provide services to persons with disabilities as an entitlement. For example, California provides annual person-centered individual program plans plus provision of all indicated care. In such cases it may not be clear what is the difference, if any, between (a) and (b) above.
- Strauss et al. carried out a series of studies in California that compared mortality in large long-term state facilities, private group homes, and the patient’s own family home (119–127). The authors found that mortality rates in the group homes and in family homes were comparable. Mortality rates in the state facilities, however, were generally lower, corresponding to modestly higher life expectancies. Reasons for the difference, which are related to quality of care, include round the clock supervision, continuity of care, centralized record keeping, and immediate access to medical attention (127).
- It is sometimes asserted that quality of care is the most important determinant of life expectancy. If the comparison is between (a) and (b) above, this assertion is incorrect: the most important determinant is undoubtedly the severity of the disability. For example, literature from many countries documents that young patients in the permanent vegetative state have mortality rates up to 500 times larger than in the general population (75, 128–136). If quality of



care is as important a determinant of mortality risk, then death rates under “standard” care would have to be 500 times higher than they would be under option (b). This is an extremely large ratio; to put it in perspective, heavy smokers are subject to mortality rates that are only 2–3 times that of the general population (137, 138).

- Researchers at The Dartmouth Atlas Project have found that more care (beyond what is reasonable and necessary) does not significantly prolong the life span of persons in the general population (139–142). Their website also provides an annotated list of 387 additional references supporting this conclusion (143).
- Finally, it may be noted that life insurance companies offer reduced premiums to persons with favorable risk characteristics, such as having ideal weight and being a nonsmoker. To our knowledge, (i) they do not give discounted rates to physicians or to the wealthy, both of whom have access to high quality health care, and (ii) life annuity underwriters do not routinely adjust for quality of care when pricing their structured settlements.

## 9. ESTIMATION OF LIFE EXPECTANCY IN INDIVIDUAL CASES

Life expectancy is an important factor in assessing the lifetime cost of future care for an individual with TBI. As we have seen, a sensible discussion requires, at a minimum, some familiarity with both the basic actuarial concepts and the relevant scientific literature. In practice, however, persons concerned with life expectancy assessment often lack this background, and as a result erroneous views are frequently advanced. We discuss some of the more significant issues below.

Much unnecessary confusion arises from the misuse of the term life expectancy when survival time is intended.

- For example, a terminally ill patient may ask the treating physician about life expectancy, but usually neither is interested in averages. Even in cases where the survival time will be limited to a few months or years, it is impossible to predict it with accuracy (144, 145). This forces the physician either to refuse to opine, and appear unhelpful, or to offer what is known about the average survival time in such cases. Even if the quoted average is appropriate, however, the patient’s actual survival time will likely be very different and the doctor will appear to be “wrong” (146, 147).
- In the legal arena, on the other hand, predictions of actual survival time are generally not required. For example, it is impossible to predict the survival time

of a normal 70 year-old male: according to government statistics 10% of such males will die in the next 4 years while another 10% will live well into their 90’s (2). But the *average* survival time — i.e., the life expectancy — is given by standard government life tables and is widely accepted by courts as the basis for compensation. It may be argued that the same reasoning should apply to persons with reduced life expectancy, including those with TBI.

- We note that if one insists upon making a prediction of survival time, then either the life expectancy or the median survival time is a possible choice. The latter has the useful interpretation of being the time at which the patient is as likely as not to be still alive. In the case of persons at high risk, such as those who are immobile and tube fed, the life expectancy is higher than the median (75).

A common misconception is that if a person’s current mortality risk is low then the life expectancy is nearly normal.

- The argument runs, for example, that although a given patient has severe epilepsy he is unlikely to die of it, and therefore “on the balance of probabilities the epilepsy will not reduce his life expectancy.” This argument again reflects confusion of life expectancy and survival time. In a very large group, *some* of the individuals will die of epilepsy, even though they are not the majority, and this reduces the *average* survival time — i.e., the life expectancy.
- An illustration of this point is the comparison of males and females. Males have life expectancies about 6 years shorter than females. It would thus be a mistake to argue that because a given 10 year-old boy is in perfect health and is currently subject to an extremely low mortality risk his life expectancy is the same as that of a 10 year-old girl.
- Further, the effect of even a moderate additional mortality risk on life expectancy is often underestimated. For example, if a 10 year-old girl has a medical condition that raises her mortality risk by only 5 deaths per 1000 persons per year for life, the result is a life expectancy reduction of 11 years.

It is often asserted that “Published studies are all based on large groups and it is impossible to predict the life expectancy of an individual.”

- Confusion of life expectancy and survival time aside, the assertion is essentially that because a scientific analysis cannot take account of *every* factor relevant to life expectancy of a given individual, *nothing* scientific can be said about an individual’s prognosis for survival.

- If this were true then standard government life tables would be irrelevant to an individual, and economists and others have been wrong to refer to them. It would also mean that life insurance actuaries and medical directors, who routinely decide whether to offer insurance to individuals and at what price, have no basis for making such decisions.

Frequently the view is expressed that high quality medical care will ensure a normal life expectancy. This is incorrect, as was discussed in the previous section.

The life expectancy literature on cerebral palsy, spinal cord injury and other conditions is extensive, and the comparison with these conditions to TBI may be helpful.

- The comparison with *cerebral palsy* (59–65) may provide a useful lower bound to the life expectancy in TBI, as persons with TBI appear to be subject to similar or slightly lower mortality risks than those with comparably severe cerebral palsy (52).

For example, the life expectancy of a 15 year-old male with cerebral palsy who can lift his head when lying on his stomach but cannot roll over or sit independently, and who is fed orally by others, has been estimated to be 22.8 additional years (62). This may therefore be a reasonable approximation to, though perhaps a slight underestimate of, the life expectancy of a similar TBI patient.

- Similarly, comparison with the *spinally-injured* patient, though imperfect, may be useful. For example, the life expectancy of a young paraplegic has been well documented to be reduced by 10 years or more (66–69). Such persons are unable to walk, but generally have unimpaired cognitive function, no bulbar dysfunction, and have normal upper body function and self-care skills with their hands. They therefore compare favorably in most respects with persons with TBI who have lost the ability to walk. (Some caveat is necessary here because spinally-injured patients are more at risk of certain medical conditions, including spinal degeneration and bowel and bladder problems.)
- For a person with TBI who is cognitively near-normal and ambulatory but still has some permanent difficulties with motor function, there is still some modest reduction in life expectancy. This may be seen by comparison with *uninjured persons who live a sedentary life style*, whose life expectancy may be argued to represent an upper bound in many cases. A permanently sedentary lifestyle is known to lead to increased risk of heart disease and other conditions (148, 149), and can be shown to lead to a reduction of about 4 years.
- Finally, if the patient has only minimal physical disability but suffers from *mental disorder or severe*

*behavioral problems*, the literature on excess mortality in such conditions may be applicable (82).

### Taking Account of Multiple Factors

Although ambulation and self-feeding are valuable predictors of expected longevity, there are other factors with some relevance. Some of these were discussed in section 5, and in addition there are refinements to mobility and self-care (can the subject roll over, sit or stand without support, carry on conversations, dress and bathe himself, etc.). Further, there are factors, such as bulbar dysfunction and hospital admissions for pneumonia, that must have some predictive value but for which there appears to be no relevant mortality data.

How can all these factors be incorporated into an estimate of a given individual's life expectancy? It is evidently not feasible to take them all into account in a scientific analysis. The rational approach is to work with the available data as far as possible – perhaps taking account of key factors such as mobility and self-care skills – and then to consider other factors for which data are not available. It may then be reasonable to argue for an adjustment, either upwards or downwards, to the evidence-based estimate. The input of a clinician can be very helpful in describing these factors and their effect on the individual's prognosis.

An alternative view is sometimes expressed: that the scientific approach should be abandoned because such an analysis cannot take account of *every* factor. Instead, a life expectancy is chosen on the basis of, for example, clinical introspection. It seems to us that this position is untenable: the existing mortality data should at least provide a *starting point* for any rational discussion.

## 10. CONCLUSIONS

An individual's *life expectancy* is the average number of additional years of life in a large group of similar persons. In many cases it can be estimated with some precision. Life expectancy should be distinguished from the individual's actual *survival time*, which is impossible to predict with accuracy, even in the uninjured general population.

We have seen that mortality is increased after TBI, many causes of death being more common than in the general population. These include pneumonia and other respiratory diseases, seizures, accidents (including choking), and – importantly – diseases of the circulatory system, related to immobility.

The key predictors of survival are mobility and self-care skills (notably, the abilities to walk and to self-feed). The life expectancy of persons who walk and self-feed is only modestly reduced by comparison with the general population, whereas nonambulatory persons with minimal

self-care skills suffer a much greater reduction. An extreme case is a gastrostomy-dependent patient in the permanent vegetative state, where the life expectancy is 10 years or less.

To estimate a given individual's life expectancy one can use the literature and existing data to account for some key predictors. Subsequently, it is reasonable to consider additional factors, which have not been taken into account, and to argue for a further adjustment. The alternative approaches of simply assuming that general population figures apply, or of proposing an estimate solely on the basis of clinical intuition, lack scientific justification and are in our view untenable. The existing population data must surely provide at least a starting point.

Finally, we note two factors relevant to life expectancy that have been insufficiently studied. The first is the prospect for improvement in function after the first few post-injury years. Although it is sometimes stated that almost all the meaningful recovery in function occurs during the first two years, it is a matter of clinical observation that substantial improvement sometimes occurs considerably later. There have been cases of persons emerging from the vegetative state after three or more years, although remaining with severe motor and cognitive dysfunction. It appears that there are no studies documenting the frequency of these late recoveries, or the degree of improvement that may occur.

Second, little is known about the decline in function of persons with TBI in old age. For example, if a young adult suffers a TBI and after several years is able to walk unsteadily and to carry on conversations with somewhat slurred speech, what can be expected in the subsequent decades, and what is the expected pattern of decline in old age? Further research on these questions would be valuable.

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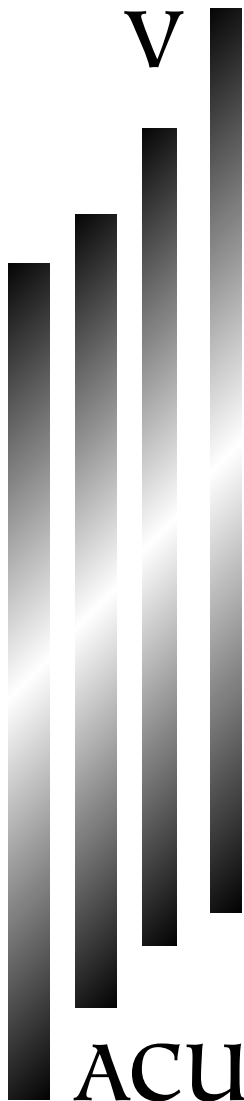
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**ACUTE CARE**



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# 18

## TBI: Pathology, Pathophysiology, Acute Care and Surgical Management, Critical Care Principles, and Outcomes

*Eli M. Baron  
Jack I. Jallo*

**T**raumatic brain injury (TBI) accounts for more than 50,000 deaths in the United States yearly and accounts for nearly 50 percent of all injury deaths (1, 2). TBI remains the leading cause of both injury death and disability among children and young adults (1). Recent observations suggest a decline in both TBI-related hospitalization and TBI-related deaths (2). This is largely due to a 40% decline in TBI related deaths in motor vehicle accidents, attributed to both the increased use of seat belts and an increase in use of safety equipment (3). Nevertheless, there remains a substantial social and economic burden related to TBI, with 1.5 million Americans sustaining a TBI yearly and 250,000 Americans being hospitalized yearly for TBI (4, 5). Of these, 80 to 90,000 people yearly experience long-term disability (6). Costs of acute hospitalization in 1997 to 1999 ranged from over \$8000 on average for moderately injured patients to over \$33,000 on average for patients with TBI requiring critical care (5). In 1995 the total direct and indirect costs of TBI in America was estimated at \$56.3 billion (7). Further, at least 5.3 million Americans (~2% of the population) live with TBI related disabilities (6). Thus TBI presents an enormous medical and socioeconomic burden and is certainly one of the leading public health problems in the United States.

A recent study reviewing the hospital discharge data over the year 1997 revealed motor-vehicle crashes, falls,

and assaults as the leading causes of injury for TBI-related discharges (27.9, 22.5, and 7.3/100,000 respectively). Rates were highest for American Indians and Alaska Natives (75.3/100,000) and Blacks (74.4/100,000), reflecting lower socioeconomic status. The age-adjusted rate for males was about twice as high as for females (91.9 versus 47.7/100,000 respectively). For both sexes, the rates were highest among those aged between 15 and 19 years and  $\geq 65$  years, reflecting increased risk taking in the younger population (e.g. drinking and driving, driving without seatbelts, etc.) and confirming that TBI is a very important health problem among the elderly (8). Another larger study confirmed an alarming increase in the rate of fall related TBI deaths in the elderly from 1989–1998 (9). A decline of nearly 50% in terms of hospitalization has been observed since 1980, that has been attributed in part to injury prevention and to changes in hospital admission practices where more patients with mild TBI are managed in outpatient settings (6, 10).

An emphasis has been made regarding the mortality rates in severe TBI falling from the 50% range in the 1970's to the 30% range in the 1990's, with a concomitant increase in the number of good to moderately disabled survivors (as opposed to those severely disabled or vegetative). This has been proposed to be due to multiple factors including improved rescue systems, enhanced emergency care in trauma facilities, rapid surgical treatment and improvement in critical care (11). One controversial area

regarding improvement in mortality statistics is intracranial pressure (ICP) monitoring and its role in the management of severe brain injury. ICP monitoring has become a cornerstone in the modern day management of severe head injury. Much emphasis has been made in terms of classifying the resultant brain injury resulting from the initial traumatic insult as primary brain injury and subsequent insults as secondary injury. Secondary injury results from entities such as hypotension, hypoxia and ICP elevation. ICP monitoring may allow clinicians to intervene earlier in terms of treating ICP elevations, which are associated with an increased mortality. A basic understanding of injury mechanisms, morphology, pathophysiology, clinical presentation, therapeutic options and expected outcomes is necessary for the clinician involved in the rehabilitation of those sustaining TBI. The present discussion focuses on the diagnosis and management of the adult with traumatic brain injury with a review of head injury morphology, pathophysiology, surgical indications, ICP monitoring, ICU care, and outcomes.

### HEAD INJURY MORPHOLOGY

Head injuries can be classified as blunt or penetrating injuries. Blunt TBI includes motor vehicle accidents and falls, and is responsible for the majority of TBI in this country. *Coup* and *contrecoup* injuries respectively refer to damage resulting from blunt trauma, where coup injuries occur adjacent to the area struck by an object and countercoup injuries occur on the opposite side, usually due to resultant acceleration of the brain after being subject to a force and striking the calvarium or skull base of the opposite side. Penetrating injuries include bladed weapons and both low velocity and high projectiles such as handguns and assault rifles. The majority of injuries are either homicides or suicides, although accidental firearms injuries contribute significantly to this number. Injury resulting from gunshot wounds occurs as a result of energy transfer from the projectile to impacted tissue. Initially, injury starts by the direct crushing and lacerating of tissues as the missile enters the skull and brain, taking with it bone and tissue fragments. A pulsating temporary cavity, with lower intracavitary pressures is formed, where the cavity may be many times larger than the diameter of the bullet. This may generate pressure waves radiating to locations away from the bullet path, causing stretching and tearing wounds (12). Penetrating injuries also carry with them a theoretically increased risk of infection, especially if bone and particulate matter enter the neural substance. Despite recent advances in neurosurgical and critical care, the prognosis for patients sustaining gunshot wounds to the head remains dismal, with an overall mortality rate of patients presenting to hospitals alive being near 60% (12).

Head injuries are further classified by their pathologic and morphologic descriptions. Skull fractures are frequently seen with head injury. The more severe the injury, the more likely the presence of skull fractures. In one series of patients sustaining TBI, 3% of emergency room attendees, 65% of neurosurgical ICU admission and 80% of fatalities sustained skull fractures (13). Skull fractures are an important entity since they carry a much higher association with intracranial hemorrhages than TBI without the presence of skull fractures (13, 14).

Skull fractures can be associated with a variety of trauma related complications. They can be a source of infection and pathologic communication with the exterior. Cerebrospinal fluid rhinorrhea results from a fracture in the cribriform plate. Otorrhea results from fractures within the mastoid air cells or temporal bone (14). These entities carry a 2–9% risk of associated meningitis (15, 16). Depressed skull fractures carry a long-term risk of late posttraumatic seizures of 31% (17). Temporal bone fractures can be associated with seventh nerve damage and/or hearing loss.

Basilar skull fractures are associated in general with greater forces than simple cranial vault fractures. Classic signs of these include raccoon eye's, representing cribriform plate fractures and Battle's sign, representing ecchymoses over the mastoid process associated with an ipsilateral skull fracture.

Cerebral contusions most commonly occur in the frontal and temporal poles adjacent to bony surfaces of the skull base, resulting from the brain striking these upon traumatic acceleration (Figure 18-1). Gliding contusions of the

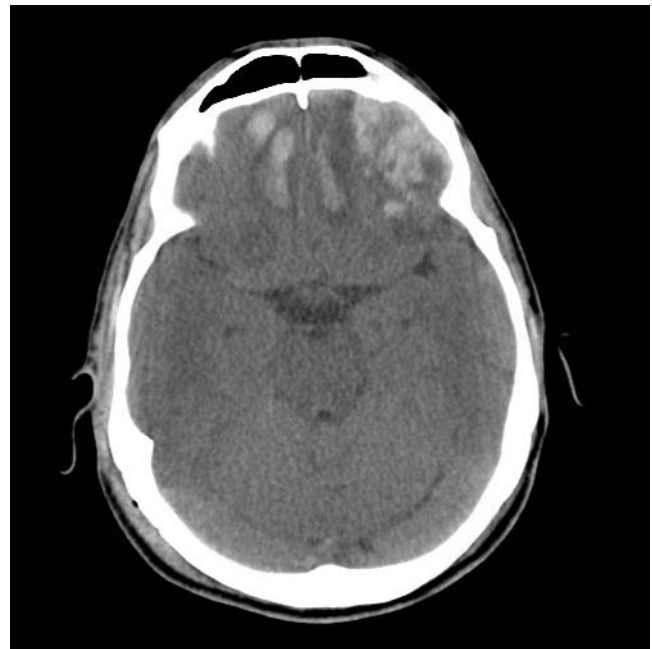


FIGURE 18-1

Axial noncontrast CT scan demonstrating bilateral frontal contusions

grey white junction represent considerably greater forces acting on the brain with associated rotational/ acceleratory vectors (14). Clinically, contusions can range from asymptomatic lesions to massive pulped areas of brain with resulting herniation. Cortical lacerations occur with penetrating injuries including depressed skull fractures.

Epidural hemorrhages usually occur in the middle fossa via laceration of the middle meningeal artery, although they can also occur in the anterior and posterior fossae. They are usually lenticular shaped and are bounded by suture lines where the pericranial layer of dura attaches to the skull (Figure 18-2). Epidural hemorrhages are most commonly associated with an overlying skull fracture (14). Though classically described with an associated lucid interval prior to clinical deterioration, only about half of patients undergoing surgical intervention present this way. These are important injuries to identify; if detected early they are usually associated with a good outcome and have a mortality of less than 10% (18).

Acute subdural hemorrhages are usually associated with a much poorer prognosis than epidural hemorrhages. This is because they often represent much more severe underlying brain damage (19). They usually result from torn bridging veins or from associated contusions hemorrhaging into the subdural space. Subdural hemorrhages tend to follow the shape of the convexities and tend to cover the entire hemisphere (Figure 18-3) (13). The present discussion pertains to acute subdural

hemorrhages in traumatic settings. Chronic subdural hemorrhages represent a different pathophysiologic condition where an initial small subdural hematoma enlarges secondary to transudative forces or repeated small hemorrhages because of associated chronic membranes. These tend to occur in older adults and are also most commonly related to an initially tearing of bridging veins.

Trauma is also the most common cause of subarachnoid hemorrhage. Often this occurs locally over convexities affected by coup type of injuries or the frontotemporal poles affected by contrecoup injuries (Figure 18-4). Subarachnoid hemorrhage from trauma can also occur in the interhemispheric fissure and in the basilar cisterns. At times it can be difficult to discern from aneurysmal subarachnoid hemorrhage, but usually the history is very suggestive of the etiology. Traumatic subarachnoid hemorrhage can result in hydrocephalus, defined as abnormal ventricular expansion with associated raised intracranial pressure (13). Hydrocephalus can also occur secondary to TBI in cases without frank intraventricular hemorrhage.

Diffuse axonal injury is a pathologic term referring to changes occurring in the brain post TBI as a result of rotational forces. The term shear injury is often used synonymously. These terms refer to classic pathologic changes including focal lesions in the corpus callosum, focal lesions of various sizes in the posterolateral quadrants of the



**FIGURE 18-2**

Axial noncontrast CT scan demonstrating a right frontal epidural hematoma. Note the lenticular shape



**FIGURE 18-3**

Axial noncontrast CT scan demonstrating a left sided acute subdural hematoma. Note that this spans the length of the convexity



**FIGURE 18-4**

Axial noncontrast CT scan demonstrating a small amount of left convexity traumatic subarachnoid hemorrhage. Note its appearance as hyperdensity adjacent to the ipsilateral sulci (arrow)

brainstem next to the superior cerebellar peduncles and microscopic evidence of widespread damage to axons (13). Though MRI imaging may hint at it, the diagnosis is a tissue based one. Diffuse axonal injury is the most commonly cited cause, in the absence of hemorrhages or ICP elevations, of prolonged depressed consciousness and of severe disability in brain injured individuals. Three grades for diffuse axonal injury are widely used: Grade 1 abnormalities refer to scattered axonal bulbs through out the white matter of the brain; Grade 2 requires the presence of a corpus callosum lesion; in Grade 3 there is the additional lesion in the dorsolateral quadrant(s) of the rostral brain stem; Grade 3 lesions nearly always result in patients being in coma or a vegetative state until death (14).

## CONCUSSION

The term concussion has been used to describe the brain injury phenomenon often resulting in very disabling symptoms following a mild to moderate TBI where no hematoma or other intracranial pathology is seen on imaging. Symptoms include headache, nausea, vomiting, difficulty concentrating, retrograde and/or anterograde amnesia and personality changes, among others. Numerous clinical definitions of this term have been used with some requiring a loss of consciousness and others not.

Even with a mild TBI, there can be widespread neuronal dysfunction and axonal injury, with the possibility of delayed axotomy occurring, all potentially contributing to the post concussive syndrome (see below)(20).

## PATHOPHYSIOLOGY AND MOLECULAR BASIS FOR INJURY

### Primary Injury

The events that occur at the moment of injury, although possibly preventable are not reversible. Brain contusions and hemorrhages, however, represent potentially avoidable causes of death and disability when evacuated promptly. These are often seen together.

### Secondary Injury

Secondary neuronal injury after TBI has received much attention with new mechanisms being elucidated and previously described mechanisms being better understood. At a macroscopic level, secondary phenomena include edema, ischemia, necrosis, elevated intracranial pressure and inadequate cerebral perfusion. At a cellular level, energy failure occurs in association with a cascade of events that contribute to secondary injury such as elevated levels of intracellular calcium, release of excitatory amino acids, generation of free radicals, and breakdown of the cellular cytoskeleton and membrane with vascular dysfunction eventually leading to cell death (21).

### Excitatory Amino Acids

The first event in this sequence is thought to be the release of excitatory amino acids; this mechanism of injury has been termed excitotoxic injury. Following brain injury, excitatory amino acids are released from injured cells. Of the excitatory amino acids, glutamate has been studied the most. Glutamate acts postsynaptically at five subtypes of receptors. These receptors are named based on the agent that specifically activates them. The NMDA (N-methyl-D-aspartate) receptor complex is an ion channel that allows passage of calcium and sodium ions. When activated by glutamate, the NMDA receptor allows calcium ions to enter the cell. Large influxes of calcium ions into neurons stimulate calcium dependent enzymes with activation of proteases, kinases, phospholipases, and nitric oxide synthase. If unchecked, these processes can eventually lead to cell death with breakdown of the cytoskeleton, free radical formation, alterations in gene expression and protein synthesis, and membrane dysfunction. Blocking the NMDA receptor improves neuronal survival in vitro and in animal models of neuronal injury (21). NMDA blockers failed to show efficacy in

recent human trials for TBI. This has been thought to be due to glutamate excitotoxicity occurring immediately at injury time but afterwards glutamate has important normal functions, such as promotion of neuronal survival. The administration of numerous NMDA antagonists in human trials may have been in the time period where glutamate had resumed its normal critical functions, rather than earlier when they would have possibly prevented excitotoxicity (22).

### Free Radicals

Free radical formation is an important part of many mechanisms of secondary injury. The most common free radicals studied are superoxide ( $O_2^-$ ), hydrogen peroxide ( $H_2O_2$ ), hydroxyl (OH), and nitric oxide (NO). Free radicals are atoms or molecules possessing an unpaired electron in the outer orbit making them highly reactive. Free iron is a key catalyst of free radical mediated injury and is readily available in injured and contused brain tissue. Free radicals damage endothelial cells and injure the brain parenchyma. This results in disruption of the blood brain barrier and is partly responsible for both vasogenic and cytotoxic edema. Once initiated, free radical injury is a self-perpetuating process with increasing damage generating more free radicals. Cells attempt to minimize injury caused by free radicals by binding them with free radical scavengers such as vitamin E, ascorbic acid, superoxide dismutase, and others. Nevertheless, these coping mechanisms may be overwhelmed in areas of significant brain injury or ischemia. Pharmacological free radical scavenging agents have been effective in reducing neuronal damage in animal models of brain injury (21). Unfortunately, a human trial of a free radical scavenger (polyethylene glycol – superoxide dismutase) in severe head injury did not demonstrate an improved outcome (23). More recently, the cannabinoid dexamabinol has been proposed as a neuroprotective treatment for head injury. Mechanistically, dexamabinol most likely works as a noncompetitive NMDA antagonist in vitro and in vivo. It blocks NMDA stimulated calcium influx in primary neuronal culture, and head injury related calcium influx in rats. In addition, it is a potent free radical scavenger (24). Recently, however, a very large multicenter, Food and Drug Administration double-blind, randomized, placebo-controlled trial of dexamabinol vs. placebo failed to demonstrate efficacy of the drug in humans (25).

### NITRIC OXIDE

Nitric oxide, a ubiquitous second messenger has been implicated in a variety of cellular processes including vascular relaxation, neurotransmitter effects, and cytotoxicity. Nitric oxide is formed by the conversion of

L-arginine to L-citrulline and nitric oxide via nitric oxide synthase (NOS). The mechanism of nitric oxide cytotoxicity is unclear, but is closely intermingled with NMDA, calcium, and free radical mediated injury. Inhibitors of nitric oxide synthase have been found to reduce neuronal injury in animal models of brain injury. A host of other mediators of secondary brain injury are under investigation including: catecholamines, adenosine, cytokines, opioid peptides, and thyrotropin releasing hormone (21).

## PHYSIOLOGIC RESPONSE TO BRAIN INJURY

### Brain Edema

The cellular mechanisms of secondary brain injury described above contribute to brain edema, and subsequently to elevations in intracranial pressure, decreased cerebral perfusion, and cerebral ischemia. Brain edema has been traditionally described as either vasogenic or cytotoxic. *Vasogenic edema* results from disruption of the blood brain barrier. The blood brain barrier is maintained by tight junctions between endothelial cells that line the vessels of the brain. Injury to these cells allows extravasation of fluid and proteins into the interstitial space of the brain parenchyma. Disruption of endothelial cells may be primary, resulting from the initial impact or subsequent hemorrhage, or secondary resulting from free radical generation, cytokines, and other secondary mechanisms of injury. *Cytotoxic* or *cellular edema* is edema of the cells themselves in contrast to vasogenic edema which is edema of the interstitial space. Cytotoxic edema results from failure of cellular ion homeostasis and membrane function. As previously mentioned, secondary injury at a cellular level results in loss of ion homeostasis and membrane dysfunction. The time course of brain edema is variable. It is thought, however, that vasogenic edema occurs early after injury and cytotoxic edema occurs in a more delayed fashion. Brain edema after traumatic brain injury is often maximal at 24 to 48 hours (26).

Edema of the brain is an important marker for injury and is also a cause of secondary injury. This is because the brain is confined by the skull, which acts as a closed container. Intracranial pressure is determined by the volume of three elements in the skull: the brain parenchyma volume, the blood volume, and the cerebrospinal fluid (CSF) volume. An increase in the volume of any of these elements will result in an increased intracranial pressure after compensatory mechanisms are exhausted. As intracranial pressure rises, there is an initial passive release of CSF into the spinal canal. There is also an innate compliance of the craniospinal axis that allows for an increase in intracranial contents without an initial increase in intracranial pressure. Once the compensatory reserve is exhausted, there is a precipitous rise in intracranial pressure (Figure 18-5) (21).

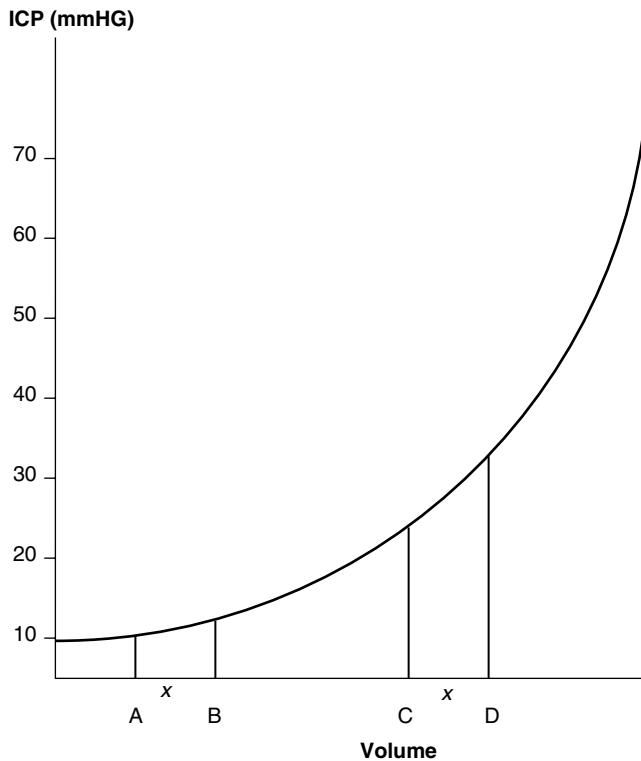


FIGURE 18-5

Pressure volume curve of the craniospinal axis demonstrating a precipitous rise in intracranial pressure associated with exhaustion of compensatory mechanisms. At a pressure of 10 mmHg a volume of  $x$  can be added with little change in ICP (represented by points A to B). Adding the same volume when the ICP is about 25 mmHg results in a much larger change in ICP (points C to D)

### Intracranial Pressure and Cerebral Blood Flow

Intracranial pressure in an adult is ordinarily under 15 mmHg. Sustained elevations in intracranial pressure above 20 mmHg are poorly tolerated by the injured brain and have been associated with increased mortality (27, 28). Sustained elevation in intracranial pressure may result in cerebral ischemia if cerebral perfusion is hampered and, if severe, can result in brain herniation. Brain herniations may occur across the falx and involve the cingulate gyrus, across the tentorial hiatus and involve the uncus, or through the foramen magnum and involve the cerebellar tonsils. Cerebral ischemia results from inadequate cerebral perfusion. The ideal degree of cerebral perfusion in the injured brain is unknown. In the uninjured brain, cerebral blood flow is tightly regulated by myogenic, humoral, and neural mechanisms to maintain a constant flow despite changes in systemic arterial pressure and intracranial pressure. This autoregulation functions over a broad range of systemic arterial pressures ranging from a lower limit of 65mmHg and an upper limit of 140mmHg to maintain

cerebral blood flow at approximately 50ml/100gms/min. If blood flow falls beneath 25ml/100gms/min then electrical activity is lost and the EEG is flat, below 12ml/100gms/min brain stem evoked responses are lost and below 10ml/100gms/min brain failure results with loss of ion homeostasis and eventual cell death (21).

### Cerebral Perfusion Pressure

It is of paramount importance that an adequate cerebral blood flow be maintained to the injured brain. Unfortunately, there is no simple technique that allows for reliable, continuous bedside measurement of cerebral blood flow. As a result, the concept of cerebral perfusion pressure is invoked when discussing cerebral blood flow to the injured brain. Cerebral perfusion pressure (CPP) is defined as the difference between mean arterial pressure (MAP) and intracranial pressure (ICP):  $CPP = MAP - ICP$ . The concept of autoregulation can be extended to discussions of cerebral perfusion pressure in the uninjured brain. Autoregulation in terms of perfusion pressure has a lower limit of 50mmHg and an upper limit of approximately 140mmHg. With a perfusion pressure below 50mmHg, cerebral arterioles are maximally dilated and perfusion cannot match the brains metabolic needs. If this state persists brain ischemia follows. As previously noted, the brain poorly tolerates ischemic conditions which aggravate secondary injury. With a perfusion pressure greater than 140mmHg, cerebral arterioles are maximally constricted and blood flow increases passively with perfusion pressure (Figure 18-6) (21).

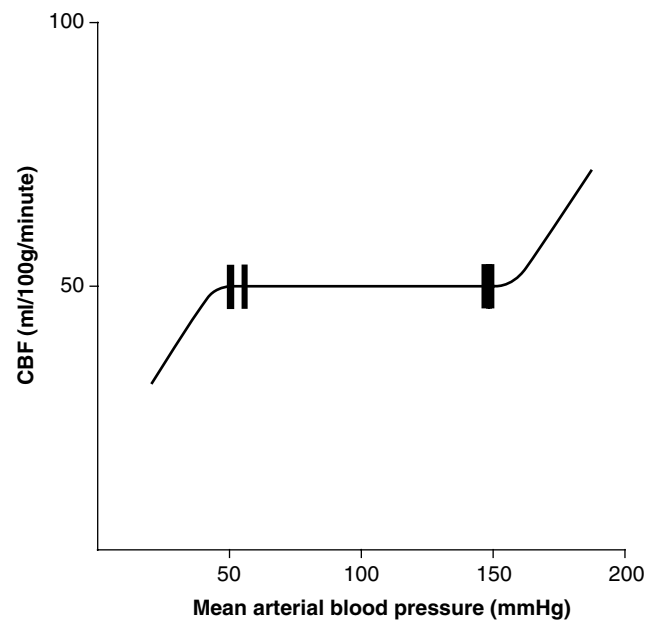


FIGURE 18-6

Autoregulation curve of the brain. Below a perfusion pressure of 50 mmHg and above a pressure of 140 mmHg blood flow passively correlates with perfusion pressure

Discussions of cerebral autoregulation are generally predicated on the brain's physiologic responses to changes in systemic arterial pressure. However, these discussions assume that the physiologic responses that are in effect in an uninjured brain are also in place after brain injury. This has been a topic of debate and study. Up to one-half of severely head injured patients will have some autoregulatory impairment. It appears as though the autoregulatory curve is shifted to the right with an increase in the lower limit at which autoregulation is effective (21). Patients with severe head injury probably require a CPP of 60mmHg to 70mmHg to maintain autoregulation of cerebral blood flow and prevent ischemic complications. In one study, outcome was shown to be significantly worse in patients with a CPP less than 60mmHg (29). Additionally, Rosner et al. (30) demonstrated more favorable outcomes when CPP was kept above 70mmHg. Current recommendations are to maintain cerebral perfusion pressure at 60mmHg to 70mmHg(31). Targeting CPP beyond 70 mmHg may increase the risk of adult respiratory distress syndrome, offsetting potential benefits from this therapy (32).

### CLINICAL PRESENTATION AND MANAGEMENT

Head injury can present in a variety of manners and often requires a high index of suspicion to be diagnosed. While loss of consciousness or altered consciousness, headaches, anisocoria, nausea/vomiting/dizziness and/or witnessed obvious traumatic injury to the head usually prompt a clinical workup, often TBI presents more subtly. All patients with a loss of consciousness or posttraumatic disturbance in sensorium should undergo CT scanning of the brain. Particular attention should be paid to intoxicated individuals, even without obvious signs of external injury. Subdural hemorrhages can easily be missed in patients intoxicated with alcohol, who may have suffered unrecognized head injuries. Further, stimulant drugs may result in TBI related agitation being overlooked. The widespread availability of CT scanning should result in a very low threshold for imaging.

Head injury can be classified as mild, moderate and severe. This is conveniently done with the aid of the Glasgow Coma Scale (GCS)(Table 18-1). Initially intended as a tool for clinicians to communicate their assessment of a patient's level consciousness in an objective matter (33), the GCS has been widely adapted as a head injury scoring system and has also proven to be an effective prognosticator with regard to clinical outcomes. Mild TBI is classified as GCS 14–15, moderate as GCS 9–13 and severe as GCS 3–8 (19).

In the field patients should have their airway status, breathing and circulation addressed first. Hypotension and

hypoxia in the field are proven secondary injury insults that are associated with poor outcomes, with hypotension being considerably more detrimental than hypoxia (34); both of these must be prevented if possible. Endotracheal intubation may be necessary in the field. Patients should have a GCS score assessed and pupillary exam prior to any sedation or paralytic being administered if possible. This can be done accurately by emergency medical personnel (35). Even if the patient has focal or lateralizing signs, such as a decreased sensorium and an enlarging pupil, current recommendations do not support ICP directed measures in the field, with the possible exception of hyperventilation in the intubated patient in neurologic extremis. Every effort to have TBI patients transported to the nearest facility possessing CT scanning, neurosurgical expertise and ICP monitoring capabilities, should be made(35). This can be most easily expedited in areas where neurotrauma systems are established. The spine should also be immobilized as there is a 4 to 8 percent association of cervical spine injury with TBI(36).

Upon arrival in the emergency room, the Advanced Trauma Life Support (ATLS) protocol, as per the American College of Surgeons, should be followed. This protocol stresses a systematic approach to trauma injury, where airway, breathing and circulation are assessed first. The assessment of the circulatory system should include attention to all sites of external bleeding including scalp lacerations which may be a source of exsanguination. Efforts should be made to control bleeding. In terms of fluid resuscitation crystalloid vs. colloid remains controversial. A recent large prospective randomized trial compared

**TABLE 18-1**  
*Glasgow Coma Scale (from Teasdale and Jennet (129))*

Eye Opening:	
Spontaneous	E4
To voice	E3
To pain	E2
None	E1
Best Motor Response	
Obeys commands	M6
Localizes	M5
Withdrawal	M4
Abnormal flexion	M3
Extensor posture	M2
None	M1
Best Verbal Response	
Oriented	V5
Confused conversation	V4
Inappropriate words	V3
Incomprehensible sounds	V2
None	V1
Score is (E + M +V) = 3 to 15	



saline to albumin in the intravascular resuscitation of critically ill patients. Similar outcomes were seen in both groups in terms of mortality and length of stay. Seven of the study population constituted patients with TBI. Mortality was increased in the subgroup with TBI receiving albumin with a relative risk of 1.62 over the group receiving normal saline (95 percent confidence interval, 1.12 to 2.34;  $P = 0.009$ ). The authors cautioned, however, that “such subgroup differences frequently occur by chance and the rate of death from any cause over a 28-day period is not considered the most appropriate outcome measurement with which to assess treatment effects in patients with brain injury (37).”

Once fluid resuscitation is addressed, a neurologic assessment is made in terms of GCS score, pupillary exam and lateralizing signs. This is preferably done prior to any sedation or paralytic being given. A lateral c-spine and chest x-ray should be performed. A CT scan is then performed as rapidly as possible in any patients with a suspected or confirmed loss of consciousness, skull fracture or abnormal neurologic/GCS exam. CT scanning has become the diagnostic procedure of choice for the initial assessment of intracranial injury. It accurately shows acute blood and identifies most skull fractures. Any coagulopathy requires correction in patients with acute blood on their CT scans.

Patients with mild traumatic brain injury who are neurologically normal with a negative head CT may be discharged home safely (38, 39). Other patients, especially those with altered mental status or collections on their CT scans should be admitted for observation and possible serial imaging. Patients with isolated skull fractures and normal neurologic exams can possibly be discharged to home, although this is controversial and must be assessed on a case to case basis (40–43).

## SURGICAL TREATMENT OF HEAD INJURY

Operative therapy is indicated in patients where intracerebral collections are exerting significant mass effect. Traditionally this has been defined as greater than 5 mm of midline shift (19). Midline shift is measured on axial CT scan images in terms of displacement of the septum pellucidum from the midline at the level of the foramen of Monroe. A line is drawn at the midline of the skull in the sagittal plane and then a perpendicular line is extended to the septum pellucidum, which is measured and recorded as shift (Figure 18-7). Mass effect is also evaluated in terms of correlation of local effect of abnormal collections on more normal appearing adjacent brain. Similarly, the basilar cisterns are evaluated for compression.

Numerous surgical criteria for a variety of commonly seen TBI related pathologies have been proposed (18). Epidural hemorrhages greater than 30 cc in volume

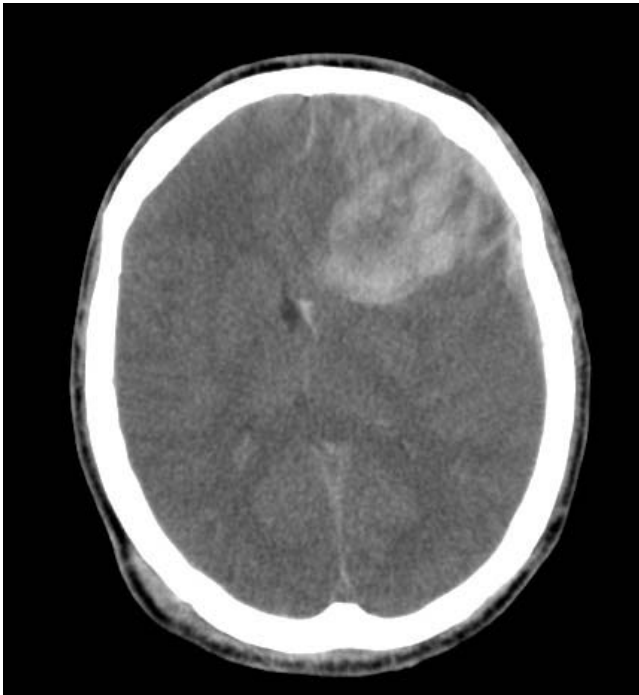


**FIGURE 18-7**

Midline shift measurement: the septum pellucidum is measured at the level of the foramen of Monroe. This scan demonstrates 1.9 cm of left to right shift

should be evacuated regardless of whether the patient is symptomatic. Those patients with a GCS score less than 9 with associated papillary dilation and an epidural hematoma should undergo decompression as soon as possible. Epidural hemorrhages less than 30 cc in volume and less than 1.5 cm in thickness, with less than 5 mm midline shift, may be managed by close observation and serial imaging in patients without focal deficits. Similarly, patients with acute subdural hemorrhages greater than 1 cm in thickness or subdural hemorrhages associated with greater than 5 mm of midline shift should undergo emergent evacuation. Smaller subdural hemorrhages may require evacuation in patients with neurologic deficits, in those deteriorating neurologically and in those with raised intracranial pressures. Both types of acute hemorrhages are best evacuated either through a craniotomy or craniectomy.

Intracerebral contusions may also be life threatening. Patients with intracerebral contusions with progressive neurologic deterioration referable to the contusion or resultant refractory intracranial hypertension should be treated operatively (Figure 18-8). Comatose patients with frontal or temporal contusions greater than 20 cc in volume with a midline shift of 5 mm and/or cisternal compression on CT scan, and those with a contusion



**FIGURE 18-8**

Axial noncontrast CT scan demonstrating life threatening left frontal intracerebral contusion which necessitated surgical evacuation.

greater than 50 cc in volume should be treated operatively. These numbers are general guidelines: patients with relatively good neurologic exams and contusions in eloquent cortex may be carefully watched, with medical treatment of ICP elevations if needed (18). Contusions are often associated with numerous other pathologic findings on CT scan such as significant cerebral edema with resultant cisternal compression and traumatic subarachnoid hemorrhage. In patients with severely contused frontal lobes with significant mass effect and resultant medically refractory intracranial hypertension, bifrontal decompressive craniectomy may be life saving; nevertheless, decompressive craniectomy for refractory ICP elevations remains a controversial area as discussed below.

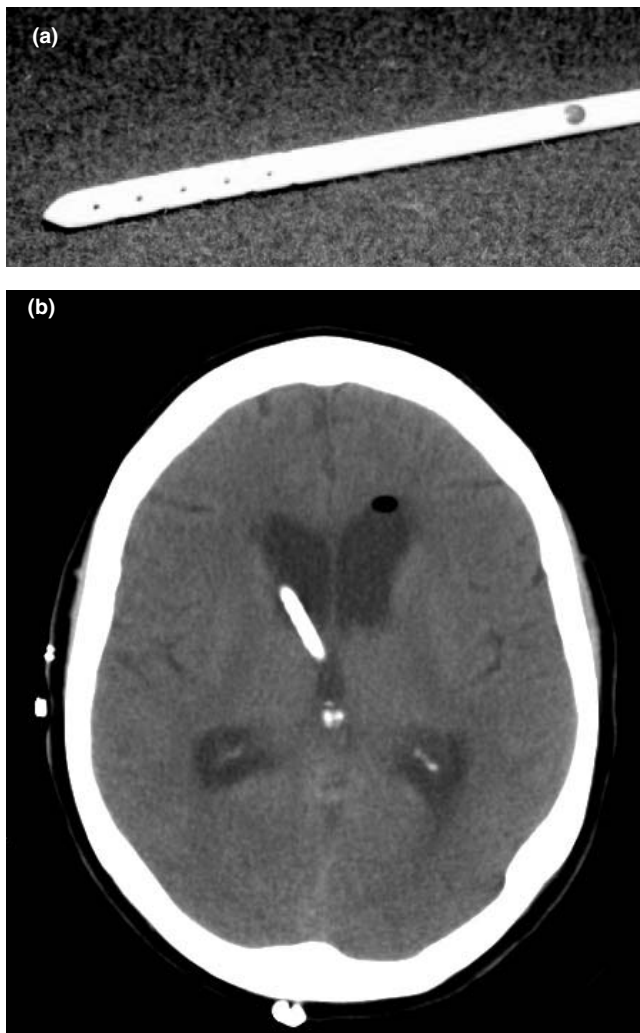
Open depressed skull fractures greater than the thickness of the skull with evidence of dural laceration should be operated on acutely to lower the risk of infection. Nonoperative management may be an option for depressed skull fracture if there is no clinical or radiographic evidence of dural penetration, no evidence of significant intracranial hematoma, depression less than 1 cm thickness, no frontal sinus involvement, no gross cosmetic deformity, no evidence of wound infection, pneumocephalus or gross wound contamination. All open skull fractures, regardless of whether managed expectantly or surgically, should be treated with antibiotics. Closed skull fractures can be managed nonoperatively.

## ICP MONITORING AND THE TREATMENT OF ELEVATED ICP

Per the Guidelines for the Management of Severe Traumatic Brain Injury (44), ICP monitoring is appropriate in patients with GCS scores post resuscitation  $\leq 8$  with a head CT demonstrating hemorrhages, contusions, edema or compressed basilar cisterns. ICP monitoring may also be appropriate in patients with GCS scores post resuscitation  $\leq 8$  with a normal head CT and 2 of the following: age  $> 40$ , motor posturing, or a systolic blood pressure of  $< 90$  mmHg. These recommendations are largely based on the landmark paper by Narayan et al. (27) which defined which patients are likely to develop ICP elevations. There is a clear association between (abnormally) elevated ICP's and mortality (28, 45). While no significant prospective study to date has demonstrated that ICP monitoring leads to decreased mortality or improved clinical outcomes, there is considerable evidence favoring its use in the management of patients with severe TBI based on retrospective series and trauma data bank studies (46–49). Nevertheless, there remains some controversy regarding the efficacy of ICP monitoring based therapy vs. empiric therapies for head injury (e.g. empiric mannitol administration)(50–52). Despite this controversy, it has become a mainstay in the critical care management of patient's with severe TBI and may also be appropriate in some cases of moderate TBI.

Ventriculostomy (external ventricular drain) insertion is the ICP monitoring procedure of choice in adults with severe TBI. It permits both monitoring of pressure via transduction of a continuous fluid column from the ventricles and also permits CSF drainage (Figure 18-9). Other monitoring technologies such as fiberoptic monitors are also acceptable but do not permit cerebrospinal fluid drainage and are subject to measurement drift (53, 54).

A threshold of 20–25 mmHg can be used to define an elevated ICP. ICP elevation presenting as a change from lower more normal pressures must always prompt a search for a potential surgical mass lesion via a repeat head CT. Elevation of the head of the bed to 30 degrees promotes jugular venous drainage and lowers ICP (55). Preventing hyperthermia can also lower ICP. While a large recent trial found systemic hypothermia ineffective in improving outcomes in TBI (56), animal models have shown it to be neuroprotective and it may play a future role in TBI management. In patients where ICP management is of concern, a mechanical airway should be in place, allowing hyperventilation and sedation/paralysis to be used as needed. Steroids have not shown to be of benefit in reducing ICP elevations and are not recommended for use in TBI. Recently, the results of a very large randomized control trial where 10008 adults with head injury and a Glasgow coma score (GCS) of 14 or less within 8 h of injury were randomly allocated 48 h



**FIGURE 18-9**

18-9(a): Ventriculostomy catheter: a silicon catheter used for measurement of ICP and ventricular drainage. 18-9(b) Axial noncontrast CT scan demonstrating ideal placement of a ventricular catheter at the foramen of Monroe

infusion of corticosteroids (methylprednisolone) or placebo were published. Compared with placebo, the risk of death from all causes within 2 weeks was higher in the group allocated corticosteroids (1052 [21.1%] vs 893 [17.9%] deaths; relative risk 1.18 [95% CI 1.09–1.27];  $p = 0.0001$ ) (57). Based on the results of this trial a recent Cochrane review on the topic concluded that steroids should no longer be routinely used in people with traumatic head injury (58).

Mannitol is a very effective drug for lowering ICP and is a mainstay in this regard. It works by dehydrating the brain, especially areas of cerebral edema and by altering cerebral rheology. Unfortunately it loses some of its efficacy with time and has some potentially serious side effects including renal failure and pulmonary edema.

Mannitol is optimally given as a slow intravenous bolus. The dose is 1 mg/kg for immediate maximum effect and duration (19). High dose therapy is preferred in the presence of acute intracranial hematoma prior to surgery (59). Smaller doses are used as maintenance therapy for ICP elevation. Mannitol's effects may be augmented by other diuretics such as furosemide. A Foley catheter must be present to help monitor mannitol's diuretic effect. Serial serum osmolalities should also be measured, where osmolalities should be kept below 320 mOsm to reduce risk of renal failure (44).

While hyperventilation was advocated in the past to lower ICP, current recommendations are more modest in terms of its use. Hyperventilation works to lower ICP by causing cerebral vasoconstriction. This reduces ICP but can also exacerbate cerebral ischemia. Hyperventilation also loses efficacy with continued use. Current recommendations are for avoidance of the use of *prophylactic* hyperventilation in the first 24 hours after severe TBI. It is reserved for treatment of patients with established ICP elevations (e.g.  $PCO_2$  30–35 mmHg) and more aggressive hyperventilation is for those patients with refractory ICP elevation and those in neurologic extremis (44, 60).

Sedation with short acting benzodiazepines such as midazolam and analgesic agents such as morphine maybe useful additional agents to manage elevated ICP. Similarly, paralytics maybe useful in the management of refractory ICP elevations. Barbiturates are considered the last line medical therapy for otherwise medically refractory intracranial hypertension. They require electroencephalogram monitoring in order to confirm burst suppression. Barbiturates have serious side effects including cardiac depression and increased infection risk. Because of barbiturates' cardiac effects, most centers use pulmonary artery catheters for hemodynamic monitoring.

In cases of medically refractory ICP elevation or in cases of significant intraoperative brain swelling decompressive unilateral or bilateral craniectomy with duraplasty has been advocated. In the operating room this decision maybe made for technical reasons (e.g. the brain is swelling so rapidly that traditional closure of the dura and bone is impossible). The use of this procedure to treat medically refractory ICP elevation is controversial. Various studies have found improved outcomes and decreased mortality in patients undergoing a craniectomy for refractory ICP vs. those medically managed (61–63). It remains to be proven, however, whether decompressive craniectomy is beneficial over maximal medical treatment.

In the presence of ICP elevation an attempt should be made to increase cerebral perfusion pressures to at least 60 mmHg in adults. CPP is defined as the difference between mean arterial pressure and ICP. In the presence of elevated ICP, cerebral autoregulation maybe deranged. Thus elevating CPP maybe critical for brain tissue at risk for ischemia. Nevertheless, it is important to remember

that ICP elevation is itself detrimental; therefore ICP elevation should never be simply treated by elevation of CPP alone. Rather, its cause should be investigated and concomitantly treated.

### CRITICAL CARE AND ADDITIONAL NEUROMONITORING TECHNOLOGIES

A brief discussion of some of the issues regarding TBI related neurocritical care is warranted. As stressed above, ICP monitoring has become a mainstay in the modern management of severe TBI. Efforts should be made to maintain CPP above 60 mmHg in patients with elevated ICP's. Knowledge of patients' hemodynamic and volume status can be very useful in the maintenance of appropriate blood pressures for CPP directed therapy. Thus a central venous catheter should be placed for central venous pressure monitoring. In patients' undergoing treatment with barbiturates, pulmonary artery catheterization is warranted. Current recommendations are for maintaining euvolemia. Intravenous fluids should be isotonic solutions such as normal saline. Dextrose containing solutions are avoided as hyperglycemia has been shown to be associated with worse outcomes in TBI (64).

Similarly, glucose abnormalities must be avoided as secondary insults. Electrolytes should be followed with at least daily laboratory studies. Particular attention should be paid to sodium values. Syndrome of inappropriate antidiuretic hormone, diabetes insipidus and cerebral salt wasting have all been described in association with TBI—all are potential sources of secondary brain injury (65).

Seizures are another potential source of secondary insult. *Early post traumatic seizures* are those that occur within the first 7 days after a TBI and *late posttraumatic seizures* are those that occur later. Early posttraumatic seizures are more common in younger people and their risk of occurrence is increased in the presence of hematomas, contusion, prolonged unconsciousness and focal neurologic signs. They are usually focal seizures with or without secondary generalization. Late posttraumatic seizures are associated with penetrating injuries, early seizures, intracranial hematomas/contusions, GCS score less than or equal to 10 and depressed skull fractures. They are usually generalized convulsive seizures(17). Current recommendations are for *prophylactic* treatment of seizures in the TBI patient undergoing craniotomy or at risk for seizures with phenytoin or carbamazepine for 1 week (17, 44, 66, 67). If late seizures do occur, they should be managed by a neurologist in accordance with standard approaches to new onset seizures(44).

Infection in the ICU setting represents a very common source of morbidity and mortality in the TBI patient population. Urinary tract infections are the most common ICU associated infection. Their most effective means of

prevention is avoiding prolonged use of catheters. Secondary to the need for mechanical ventilation for a majority of these patients, and also their reduced airway protection mechanisms, pneumonia in the severe TBI patient population is the second most common nosocomial infection and the most common infectious cause of death (68). Several authorities have recommended early tracheostomy in these patients to promote pulmonary toilet, reduce infections and decrease length of stay in the ICU (69, 70). Aggressive attention to suctioning and maintaining the head of the bed elevated while administering tube feeds to minimize aspiration risk are mandatory as is strict hand washing (68). Immobile patients should be rolled every two hours to minimize the risk of skin breakdown. Early removal of patients' cervical collars may further avoid another source of decubitus ulcers (71). Perioperative antibiotics should be administered for trauma craniotomies (68). Additionally, antibiotic coated ventricular catheters may reduce infection rates in patients needing prolonged monitoring (72).

Nutrition should be initiated early in the critically ill TBI patient. This is preferably through a small intestine tube, with feedings starting within 2 to 3 days of injury (73, 74). Caution must be exerted when inserting nasal feeding tubes, as anterior skull base fractures may allow passage of the tube intracranially (75, 76). Nutritional needs in the TBI patient have been estimated to increase 40 percent over that calculated for uninjured people of similar age, sex and height. This is due to numerous factors including hormonal factors, cytokines and movement occurring post TBI. Despite high protein intake and appropriate caloric provision, during the early period post TBI, positive nitrogen balance cannot be achieved. A nutritional goal in the ICU should be the maintenance of adequate caloric and protein intake in an effort to improve nitrogen balance (77). Every severe TBI patient should have a formal nutrition assessment by an appropriately trained dietician. Markers such as prealbumin, nitrogen balance and liver function tests should be followed regularly. Gastrointestinal prophylaxis should also be routinely used in order to minimize the risk for stress ulcers.

Deep venous thrombosis is a common complication in the critically ill TBI population, with as many as 53.8% of patients experiencing this complication (78). Patients should have sequential compression boots and subcutaneous heparin used whenever possible. The safety of both subcutaneous heparin injections and low molecular weight heparins started early (within 24 to 72 hours) in severe TBI has been demonstrated (79, 80). Deep venous thrombosis should also be considered as source of fever. In cases of established thrombosis where anticoagulation is contraindicated, inferior vena cava filter placement should be considered.

Additional neuromonitoring technologies are used in selected centers. These include jugular bulb venous

saturation monitoring, cerebral blood flow monitoring and regional tissue oxygen tension monitoring, among others. Jugular venous oxygen saturation monitoring is intended to detect increases in oxygen consumption (decreased jugular oxygen saturation) and as a result globally increased oxygen extraction by the brain. It is measured by placing a catheter tip (equipped with a fiberoptic monitor) in the dominant jugular bulb and is reserved for patients with severe TBI. Current recommendations are to maintain jugular venous saturation between 55% and 75%, with this range intended to allow for a margin of error. Desaturations below 50 percent are associated with significant increases in patient mortality (81). Any reported desaturation must be confirmed by a jugular venous bulb blood sample being sent for analysis to confirm the reading. If a desaturation is confirmed, a workup is pursued to find its cause in an effort to reverse any potential secondary insults contributing to the desaturation, including overly aggressive hyperventilation (82).

While jugular venous oxygen saturation monitoring may be reflective of global oxygenation, regional oxygenation is better measured by brain tissue oxygen tension monitors (83). These monitors can be inserted in normal brain or preferably in the penumbra of an intracerebral lesion. Therapy then can be directed towards improvement of cerebral oxygenation (84). Brain tissue oxygen tension monitors can be placed safely and they reliably measure oxygen tissue tension adjacent to insertion sites. Because brain tissue hypoxia has been related to poor outcomes, efforts should be made to prevent this. The effects of tissue oxygen tension directed therapy need to be studied further before this modality is globally recommended (85).

Various centers routinely use a host of methods to measure cerebral blood flow, which are considered experimental techniques in the management of severe TBI. These include intermittent measurement techniques such as xenon techniques (including inhalational, intravenous and xenon/CT scanning), nitrous oxide saturation techniques, single-photon emission tomography (SPECT) and positron emission tomography (PET) scanning, gradient-echo echo planar imaging (EPI) using magnetic resonance imaging (MRI) technology and transcranial doppler (TCD) monitoring. Other techniques measure continuous regional cerebral blood flow such as laser-doppler flowmetry and thermal diffusion flowmetry. Cerebral blood flow measurement represents a method of assessing brain function in an objective manner. In non-pathologic conditions, cerebral blood flow and brain metabolism tend to be coupled. Thus increased cerebral metabolism tends to increase cerebral blood flow and vice versa. In patients sustaining TBI, however, this coupling is retained only in 45 percent of cases (86). Reduced cerebral blood flow has been associated with worse neurologic outcomes (87, 88). Further, global cerebral blood flow may be different than regional blood flow (89),

misleading a clinician to think that perfusion is adequate when critical structures are being under perfused. These technologies may actually allow a clinician to make management decisions resulting in a different maneuver than routine ICP directed therapies alone (which could potentially worsen regional blood flow related secondary insults)(90). The routine use of global and regional cerebral blood flow measuring technologies has yet to be widely accepted.

Another potentially useful monitoring modality in the management of severe TBI patients in the ICU is continuous electroencephalography (EEG) monitoring. EEG can detect both convulsive and nonconvulsive status epilepticus, which often is an unsuspected cause for altered consciousness in patients with severe TBI. In one series nonconvulsive status epilepticus was demonstrated in 11% of patients (91). It may be associated with poor outcomes (92). Continuous EEG monitoring is also mandatory in the monitoring of barbiturate therapy.

## OUTCOMES FROM TRAUMATIC BRAIN INJURY

Mild traumatic brain injury is noted for very often having an association with the troubling postconcussive syndrome. This can be described as having three categories of symptoms. These include cognitive complaints (e.g. decreased attention, poor concentration), somatic symptoms (e.g. headache, tinnitus, light sensitivity, etc.) and affective complaints, such as depression or irritability. These symptoms occur in 80 to 100% of individuals post mild TBI. These are paralleled by deficits in cognitive testing, with impaired speed and information processing and decreased performance on tests of memory and attention. At three months post injury, symptoms have resolved in two thirds of patients (20). Complicating the matter, many physicians are skeptical about the post concussive syndrome's existence, where often litigation is considered as a motive for continued symptoms. While secondary gain should always be considered in this group of patients, the majority of patients with post concussive symptoms have symptoms independent of litigation. Regardless of litigation, patient's with post concussive syndrome tend to have their symptoms improve with time (93). Despite the tendency for improvement with time, some people experience long term disability related to mild TBI including depression, sleep disturbances, post traumatic stress disorder and anxiety (20). A clinical evaluation by a neuropsychiatrist specializing in TBI can be very useful here where a combined educational and, if necessary, pharmacologic approach may prove beneficial.

Most patients with moderate TBI tend to improve neurologically. In one series following 79 patients, 67% of patients improved to GCS 15 by time of discharge.

At an average follow up of 27 months, Glasgow outcome scores (see below) were rated as good or moderate disability in the majority of survivors of moderate TBI, but only 74% of these patients who were employed prior to their TBI returned to work. The majority had significant cognitive and functional deficits, including memory problems, concentration difficulties and headaches, among others (94). Other reports have confirmed good recoveries in terms of general outcomes at 3 months but few patients are actually symptom free. When compared to patients who sustain mild TBI, those with moderate TBI recover less completely and more slowly. Patients tend to have difficulty with memory function and as many as 50 percent have some emotional or behavioral difficulty at 1-year post injury (95).

The mortality from severe TBI has fallen from the 50% range in the 1970's to the 30% range at present date. This is likely due to the implementation of prevention measures, safety legislation, public education initiatives, further improvements in and wider availability of emergency medical systems and regional trauma centers. Improvements in neurocritical care and the implementation of evidence-based treatment guidelines for severe head injury patients may also be responsible for improved survival rates(96). Advances in prehospital care may be contributing substantially to lower TBI mortalities. In San Diego county, California, from the years 1980 to 1982 there was a decline the head injury death rate by 24%. Similarly, the number of patients listed as dead on arrival at hospital emergency facilities decreased by 68%. This is believed to be due to a concurrent marked improvement in the county's ground and air emergency medical system(97). Becker et al. demonstrated a mortality in the 30% range in severe TBI patients managed with modern neurocritical care principals, including ICP monitoring, when compared with same era management at other institutions resulting in a mortality in the 50% range (47). Other series report similar mortalities from severe TBI in patients undergoing aggressive neurocritical care management(98, 99). Further, in patients with severe blunt TBI surviving beyond the emergency room, the mortality rate across the state of Pennsylvania for the years 1995–2000 was 34% for those undergoing ICP monitoring, while those managed without monitors had an overall mortality rate of 43% (100).

Numerous factors have been established as predictors of mortality in severe TBI. These include hypotension, hypoxia, decreasing GCS score, decreased GCS motor score, increased age, increased injury severity score, bilateral unreactive pupils, and abbreviated injury severity score of head among others. Head injury characteristics on CT have also been used as prognosticators regarding mortality in severe TBI. These include compression of the basilar cisterns, presence of traumatic

subarachnoid hemorrhage, presence of midline shift and the presence of other intracranial lesions on CT (31).

Though numerous studies have focused on predicting mortality in patients' with severe TBI, as survival improves, the focus of outcome assessments must be directed towards quality of survival and any residual disability. In this direction the term 'functional outcome' is gaining acceptance.

The World Health Organization (WHO) model of disease impact provides guidance as to the direction of outcome measures (101). This model identifies four areas in which an injury can be assessed: pathology, impairment, disability and handicap. Pathology is the most well known area to the acute care physician. It is determined by the lesion characteristics. These include location, hemorrhage, diffuse axonal injury, and elevated intracranial pressure among others. Impairment in the TBI patient refers primarily to the neurological deficits, but associated problems may have an impact on the level of impairment. For example, a patient with significant orthopedic injuries may have weight bearing limitations that contribute to the level of impairment. Disability and handicap outcomes are more familiar to rehabilitation specialists. These domains make up some of the major long-term limitations for the TBI patient (102). Disability is usually described in terms of activities of daily living (ADL). A number of measurement tools have been developed to assess this area. These include the Glasgow Outcome Scale (GOS), the Disability Rating Scale (DRS) the Functional Independence Measure (FIM), the Functional Status Examination (FSE), socioeconomic measures, quality of life measures and caregiver burden measures.

The GOS is frequently used in the neurosurgical literature. It was created in an effort to provide a global assessment of disability post severe TBI. The GOS has 5 categories: good recovery, moderate disability, severe disability, vegetative state, and death (Table 18-2) (103). Good recovery and moderate disability are generally grouped together as favorable outcomes, with the other 3 categories making up the poor outcomes. It is a fairly reliable measure but lacks sensitivity due to its broad categories. Nevertheless, at 6 months post injury the GOS has been shown to correlate well with neuropsychological, psychosocial, and vocational functioning (104).

The DRS was developed as a quantitative instrument for assessing outcomes in severe head trauma. It was designed to be easily learned, be quickly completed, be valid and have high inter-rater reliability. It consists of 8 items divided into 4 categories: 1. Arousal and awareness; 2. Cognitive ability to handle self-care functions; 3. Physical dependence upon others; 4. Psychosocial adaptability for work, housework, or school. Scores range from 0, which signifies no disability to 30, which indicates death (105). The DRS is widely used as an outcome assessment. It has shown good reliability, better precision

**TABLE 18-2**  
*Glasgow Outcome Scale (from Jennet and Bond (103))*

5	<b>Good Recovery:</b> resumption of normal life even though there may be some persistent neurologic and psychological deficits
4	<b>Moderate Disability:</b> disabled but independent. Though these patients may have considerable neurologic deficit (e.g. hemiparesis) they can travel independently and work in sheltered environments
3	<b>Severe Disability:</b> conscious but disabled. These patients are dependent for daily support due to physical or psychological limitations
2	<b>Persistent Vegetative State:</b> Unresponsive and speechless individuals who have sleep wake cycles
1	<b>Death</b>

than the Glasgow Outcome Scale, and greater reliability than other measures (106).

The FIM is an 18 item, 7 level scale that rates the ability of person to perform independently in self care, sphincter control, transfers, locomotion, communication and social interaction. The scores range from 18 (minimally dependent) to 126 (maximally dependent). The score can further be divided by two subscales, motor (the sum of 15 components of the scale) and cognitive (the sum of 8 components of the scale)(10). While showing good reliability for spinal cord injury as an overall assessment of self-care and mobility, it is also useful for assessment of functional outcomes post TBI (106).

The FSE was developed to evaluate functional changes as a result of TBI. It covers physical, social, and psychological domains. The FSE consists of data gathered through a structured interview and is scored from 0–28, where 0 signifies no change from preinjury, 27 maximum dependence on others and 28 death. The FSE is significantly related to important constructs such as family burden, significant other depression, and sacrifices the family makes, as well as overall indices of recovery and satisfaction with level of functioning. The FSE correlates with overall recovery and patient level of satisfaction significantly better than the GOS (107).

Functional outcomes in patients sustaining severe TBI vary by report but overall ~ 30% are reported as having good outcome on the GOS at 1 year. In 1977, Becker et al. reported patients surviving severe TBI. At 3 months or more post injury, 36% made a good recovery, 24% were moderately disabled, 8% were severely disabled, 2% were vegetative and 30% were dead (47). Jiang et al. (108) studied 846 patients with severe TBI and at 1-year reported good recovery in 31.56%, moderate disability in 14.07%, severe disability in 24.35%, vegetative

status in 0.59%, and a 1-year mortality of 29.43%. Rudehill et al. (109) reported data from the Karolinska institute regarding severe TBI in terms of GOS “when no further improvement could be anticipated. This final condition usually occurred 3–12 months after injury.” Forty one percent of patients with GCS scores 3–4 post resuscitation had GOS scores of 4–5, 21% had GOS scores of 2–3 and 38% had a score of 1 (death). Of patients with a GCS 5–8 post resuscitation, 70% had a GOS score of 4–5, 17% had a score of 2–3 and 13% had a score of 1. Data from the Trauma Coma Databank revealed GOS scores in patients sustaining severe TBI of 4–5 in 43%, 2–3 in 21%, and 1 in 36% (110). The European Brain Injury Consortium survey revealed GOS score in patients with severe TBI at 6 months post injury of 4–5 in 45% 2–3 in 19% and 1 in 36% (111). Thus, in modern series, the majority of severe TBI patients have favorable outcomes, with few patients surviving with severe disability or in vegetative states.

Nevertheless, few patients sustaining severe TBI return to their premorbid functioning and the majority have significant cognitive and emotional sequelae (112). Tate et al. (113) found that 75% of patients surviving severe TBI have major disability in terms of reintegration with regards to employment, interpersonal relationships, functional independence, social contacts and leisure interests. Even among those with GOS scores of good recovery and moderate disability, only 50% had good psychosocial reintegration. Another series found a 70% unemployment rate at 1 year and a 24% rate of depression following severe TBI. Of these patients, impatience was the most frequently described behavioral problem. Thirty percent of these patients had returned to live with their parents, and relationship breakdown occurred for 38% (114). In another series looking at patients at 3 years follow up, though only 5% of the patients had a GOS of 2 or 3, half of surviving patients were noted to have social handicaps and 78% were noted to have neuropsychological impairment. Half of these patients suffered from headaches (115). Severe TBI patients continue to experience significant cognitive difficulties at 1-year post injury. Kersel et al. (116) followed 65 patients with severe TBI and assessed their GOS and neuropsychological outcomes at 6 months and then at 1 year. They assessed pre-morbid intellectual level, current level of general intellectual functioning, simple and complex attention, verbal memory, executive functioning and perceptual functioning: despite 51% of patients having a good recovery and 20% having moderate disability on the GOS, at best 31% and up to 63 percent had difficulty in neurocognitive tests administered 1 year post injury. Impairment was most frequently seen in verbal memory tests, complex attention tests and executive functioning. General intelligence and perception were among the areas least affected 1 year post-injury.

Depression, decreased social contact and loneliness remain persistent long-term problems for the majority of individuals with severe TBI (117). Hoofien et al. (118) assessed 67 patients at 10 to 20 years post TBI and noted serious psychiatric symptoms in this group. About half the patients had problems with hostility including temper outbursts and poor self control. Depression and anxiety were also very common. The psychological and emotional consequences of severe TBI present an enormous caregiver burden. Despite a high incidence of physical disability and cognitive impairment in severe TBI patients at 1 year, the presence of emotional difficulties may cause the most stress for care givers. Anger, dependency and apathy were all found in one series to be the most difficult emotional problems (in severe TBI patients) for caregivers to deal with; over one third of caregivers were found to have clinically significant anxiety and depression and over one quarter reported impairment in their own social adjustment such as problems in their marriages or continuing employment (119). Psychosocial problems and difficulties with re-entry into the community thus represent a major challenge in the rehabilitation of patients sustaining severe TBI (117).

### THE ROLE OF THE REHABILITATION SPECIALIST IN PATIENTS SUSTAINING TBI

The rehabilitation specialist plays a pivotal role in the treatment of those sustaining TBI. While emergency medical service personnel/paramedics, emergency physicians, trauma surgeons, neurosurgeons and critical care specialists may be involved in the initial encounter and acute inpatient management of patients sustaining TBI, the rehabilitation specialist is essential in directing appropriate rehabilitative services to the patient sustaining brain injury. For mild TBI, a single early intervention may be appropriate or more intensive services involving neuropsychiatric intervention may be needed in some cases (20, 120).

For more severe TBI, extensive rehabilitation is often needed. This may be better started off early rather than later, with resultant improved mobility and decreased length of acute rehabilitation stay (121, 122). Intensive rehabilitation may also improve early functional outcome of TBI patients (123).

Acute rehabilitation for patients with severe TBI starts in the comatose and early arousal states, with the goals of preventing orthopedic and visceral complications. Subsequent inpatient rehabilitation is designed to help impairments recover and to teach patients to compensate for their disabilities. This includes both psychological and physical therapy. A third phase, and perhaps most difficult, is therapy "for achieving physical, domestic and social independence, reduction of handicaps and

re-entry into the community (124)." One controversial area is sensory stimulation which is intended to accelerate recovery or arousal in patients who are comatose or vegetative. There is little evidence to support or to challenge this practice (125).

Rehabilitation specialists need to be aware of the possible causes of readmission to acute care for patients sustaining TBI, including the possibility of patients requiring further neurologic workup. During the first year post TBI, the most common reasons for rehospitalization include orthopedic or reconstructive surgery, followed by infectious disorders and general health maintenance. After the first year, seizures and psychiatric problems represent a considerable portion of admissions (126). In the case of new onset post traumatic seizures, a detailed workup with neurologic consultation should be pursued. Posttraumatic hydrocephalus may be another problem seen late after TBI. Symptoms include arrest in clinical progress, dementia, gait disturbance and incontinence (127). The threshold to obtain a repeat CT scan should be low in the TBI patient with any neurologic deterioration. It should be kept in mind that even after one year post injury, patients sustaining severe TBI may significantly benefit from inpatient rehabilitation (128).

### Conclusions

TBI remains an enormous problem despite advances in its management in the last 30 years. It represents a tremendous social and economic cost. The patient experiencing head injury should be evaluated in a systematic manner with attention being paid to the possibility of the presence of a mass lesion. This may mean the need for a mechanical airway, decompressive surgery and the possibility of ICP monitoring. Hypotension and hypoxia, in addition to elevated ICP, are critical secondary insults that must be avoided if possible. Outcomes from TBI continue to improve but are still hampered by significant psychological, cognitive and economic disability in survivors. The rehabilitation specialist plays a key role in the care of patients post severe TBI by being involved in acute care, inpatient rehabilitation, outpatient treatment, and, ultimately, societal reintegration.

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# 19

## Assessment, Early Rehabilitation Intervention, and Tertiary Prevention

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**A**n estimated 5.3 million Americans live with a combination of chronic physical, cognitive and neurobehavioral impairments secondary to traumatic brain injury (TBI) that adversely affects daily function, social participation and/or quality of life (1). The annual economic impact for the direct care of TBI survivors, excluding inpatient care, has been estimated at \$25 billion.<sup>1</sup> Also, the annual incidence of TBI is estimated at 180–220 per 100,000 population. As the subsequent fatality rate is estimated at 10%, that suggests that approximately 550,000 persons are hospitalized annually in the United States with brain injury. The vast majority of survivors with a mild TBI are expected to have a good recovery, but as many as two thirds of survivors with a moderate TBI and approaching 100% of severe TBI survivors are left with permanent impairments and disabilities (1–2). It is apparent that the societal impact of TBI will continue to grow when one considers these statistics together with the observation that TBI primarily occurs in young adults.

Some of the impairments and disabilities after TBI can be attenuated by tertiary preventative measures such as early and adequate treatment directed at arresting the ongoing injury process, preventing complications and by the early use of comprehensive rehabilitative interventions. The role of early and comprehensive rehabilitation in achieving these goals is increasingly supported in the neuroscience

and neurorehabilitation literature that studies aspects of brain plasticity in both animal models and clinical paradigms. These areas of research have documented the importance of enriched environments and physical activity to neurogenesis and cell survival (3). Animal and clinical studies have also documented the negative impact on outcome secondary to chemical and physical restraints relative to participation in rehabilitation (3–5).

The initial psychiatric evaluation of a traumatic brain injury survivor should, therefore, ideally occur within the first twenty-four hours of the event. That is, rehabilitation should no longer be considered the final stage of the recovery process but rather rehabilitative assessment and intervention should be implemented during the acute recovery period and continue through the subacute and chronic stages for a comprehensive rehabilitation program that maximizes functional outcome. Indeed, a small yet compelling body of evidence continues to evolve supporting the concept that early application of rehabilitation strategies shortens the length of hospitalization and enhances the quality of outcome (3,6,7).

The issues that a psychiatrist needs to consider during the initial evaluation of a patient with a moderate to severe traumatic brain injury include: 1) an assessment of residual impairments, 2) an estimation of prognosis, 3) initiation of early rehabilitation intervention emphasizing preparation for ongoing rehabilitation needs and prevention of complications, and 4) formulation of a long-term

treatment plan that will address the rehabilitation and reintegration needs of the survivor. This chapter will review those issues that are most germane to the physiatrist during the acute care phase of intervention after a traumatic brain injury.

## ASSESSMENT

### Residual Impairments

The impairments incurred secondary to a severe traumatic brain injury can be broadly categorized as physical, cognitive and neurobehavioral. Potential impairments are numerous and have been comprehensively reviewed elsewhere. (8) A thorough documentation of all impairments and deficits during the initial physiatric evaluation is often neither practical nor possible in a coma emerging patient where arousal, awareness or communication may be compromised. However, attention should certainly be directed to those impairments that have prognostic implications and those that have an impact upon the immediate rehabilitation strategies. Because the majority of traumatic brain injuries result from motor vehicle accidents, (9) associated injuries that can have a significant impact on survival and functional outcomes are found in 60% of patients (10–12). Hence, it is incumbent upon the rehabilitation team to be cognizant of medical issues such as fractures, that may have been undetected during the acute stabilization (10).

The physical consequences of neurotrauma most critical for assessment and early intervention are those that effect swallowing, communication, mobility and locomotion. Preliminary swallowing evaluation and treatment recommendations can be done at bedside while the patient is still in the intensive care unit and completed as the patient becomes more alert. The establishment of a consistent communication system is a prerequisite for determining the extent of cognitive deficits and thus appropriate rehabilitation interventions. Disorders affecting mobility and locomotion are often the primary focus of the family and render the survivor at risk for secondary complications.

Cognitive deficits have a greater impact on functional outcome than the residual physical deficits in longitudinal studies (13). However, the specific cognitive deficits that most profoundly effect long-term outcome remain to be determined through further research. Thus, the cognitive skills most appropriate for screening during the initial assessment are those that effect communication and the ability to learn basic functional skills.

Neurobehavioral sequelae of severe traumatic brain injury can have similar global effects in all functional spheres and may have the greatest impact in long-term outcome (8). Agitation, the most dramatic behavioral disorder

observed in the coma emerging brain trauma survivor, has significant impact on the initial type of rehabilitation services. Both the presence and presentation of agitation have long-term prognostic implications (14,15).

### Prognosis

Predicting outcome after TBI serves several practical purposes. Estimating prognosis permits the development of a more meaningful individualized rehabilitation plan. The family and subsequently the patient benefit from the prognostic information as part of their adjustment to the catastrophic event. Finally, the ability to accurately predict outcome is important for program evaluation purposes and in designing studies targeted to influence functional outcome. To date, the studies designed to identify significant prognostic variables have resulted in two general observations. First, no single variable is adequate to predict an outcome from an injury as complex and heterogeneous as TBI. Second, the importance of prediction variables is predicated on the outcome of interest. For example, injury severity variables predict rehabilitation readiness and, to some extent, rehabilitation outcome, but these variables are less robust at predicting vocational outcome (2,6,16–19). Similarly, vocational outcome prediction involves knowledge of premorbid, social and disability variables that are not immediately critical to the early assessment of the TBI survivor (17–19).

At the initial physiatric evaluation, a number of prognostic variables are available that include premorbid, injury severity, impairments and functional characteristics (Table 19-1) (2, 20–22).

Age at the time of injury appears to be the most powerful premorbid prognostic indicator of both mortality and functional outcome. Studies stratifying severe TBI patients at 50, 60, 65 and 70 years of age have consistently shown that mortality dramatically increases with increasing age. This prognostic indicator remains significant even when the severity of the injury is controlled for by using the Glasgow Coma Scale (GCS), the Injury Severity Scale, or other measures of trauma severity (23). Mortality as high as

**TABLE 19-1**  
*Early Predictors of Outcome*

Age
Primary brain injury
Secondary brain injury
Glasgow Coma Scale
Pupillary response
CT scan
Sitting balance
Functional Independence Measure
Post-traumatic amnesia

79% has been described in patients greater than 60 years old, and 33% has been described in those under 40 years of age (6). This same study compared outcome at 6 months and found that a good outcome in the greater than 60 years old group was limited to 2%. In the under 40 years old group, 38% had a good outcome. Finally, age remained a significant prognostic indicator even after controlling for past medical history (24).

The type of central nervous system lesion incurred at the time of trauma has been correlated with both survival and functional outcome. For example, the presence of a mass lesion implies a higher mortality and a poorer functional outcome (2,25). Most studies agree that the injury with the highest mortality rate and the poorest functional outcome is the subdural hematoma (25,26). Other acute computed tomography (CT) scan changes that carry prognostic implications include the presence of third ventricle and/or basal cistern abnormalities, implying raised intracranial pressure in excess of 20 millimeters; the functional outcome of survivors with this acute CT scan finding remains poor at 6 months post-injury (27). Temporal lobe lesions, with a resulting midline shift of more than 4 millimeters, carry negative prognostic implications for both survival and functional outcome (28). Finally, basal ganglion hemorrhages are rare CT abnormalities after a severe traumatic brain injury. As a primary lesion, basal ganglion hemorrhages carry a fairly good prognosis with the majority of patients achieving a moderate or good functional outcome (29).

The most comprehensive assessment of the predictive value of early CT scan findings and functional outcome at one year looked at 849 patients who were admitted to inpatient rehabilitation and followed for 1 year (20). This observational study found that a midline shift of greater than 5 mm or a subcortical contusion resulted in greater assistance requirements for activities of daily living (ADL), ambulation and supervision, whereas, bilateral cortical contusions were associated with significant global supervision needs but not ADL or ambulation assistance needs (20).

Both coma duration and coma depth are important markers of injury severity with prognostic implications, but coma duration may be a better predictor of motor and cognitive recovery than coma depth (30–33). Coma duration and outcome, assessed by the Glasgow Outcome Scale, have been found to be correlated in that functional outcome is proportionately worse at 1-year post injury with increasing length of coma and patients who remain comatose for greater than 2 weeks rarely achieve a good recovery (34). At the other end of the spectrum, coma durations as little as 1 hour have also been found to effect outcomes such as subsequent employment (34). This relationship between coma duration and outcome is more prominent with diffuse axonal injury and appears somewhat linear in that there is no clear cut-off that predicts outcomes assessed by the Glasgow Outcome Scale (30).

Coma depth, as measured by the Glasgow Coma Scale (GCS), has been an important prognostic indicator of mortality and to a lesser extent, outcome. Glasgow Coma Scale scores during the first 24 hours post-injury appear to be better predictors of survival than scores after the first 24 hours, but GCS scores 2–3 days post-injury are better predictors of functional outcome. A review of the prognostic importance of the Glasgow Coma Scale by the Brain Trauma Foundation concluded that there is an increasing probability of poor outcome with decreasing GCS scores in a continuous stepwise manner (2). However, most of these studies collapse the Glasgow Outcome Scale into two or three outcome categories; the predictive value of the initial GCS score is poor when trying to be more precise in using all five Glasgow Outcome Scale variables (2). Early GCS scores have limited prognostic value for acute inpatient rehabilitation outcome. The initial and lowest 24-hour GCS score has limited value as a predictor of rehabilitation admission and discharge Rancho Los Amigos Levels of Cognitive Functioning Scale, Functional Independence Measure and Disability Rating Scale scores (35). Another study found that the GCS score did not predict the degree of improvement in the Functional Independence Measure score during inpatient rehabilitation (36). A more recent analysis of GCS scores found that the admission GCS score during a period between 1997 and 2001 was not as predictive of the Glasgow Outcome Scale score at six months post-injury as had been observed between 1992 and 1997 (37). These data appear to reflect a change in the early management of TBI patients with more aggressive resuscitation. For prognostic purposes, GCS scores should be obtained after the patient has been resuscitated and after pharmacologic sedating and paralytic agents are metabolized (2).

The duration of post-traumatic amnesia (PTA) is thought to have an even stronger relationship with outcome than depth or duration of coma. Periods of post-traumatic amnesia ranging from 1 hour to several days have resulted in impairment of divided attention as determined by the Paced Auditory Serial Addition Task (PASAT) that persist for 15 and 40 days post-injury, respectively (30). The duration of post-traumatic amnesia has also been found to be predictive of functional outcome as measured by the rehabilitation admission and discharge Functional Independence Measure and Disability Rating Scale scores (22). Data from the International Data Coma Bank have demonstrated that less than 2 weeks of PTA resulted in 80% of patients achieving a good recovery and 0% remaining in the severe disability functional outcome category; after 4 weeks of PTA, functional outcome diminished to 27% achieving a good recovery and 30% remaining severely disabled (34). Others have demonstrated that greater than 4 weeks of PTA results in virtually no patients achieving a good recovery. After 12 weeks of PTA, severe cognitive deficits

and a very poor prognosis for functional independence at 1 year are observed (30). As a caveat, the importance of PTA duration on functional prognosis is most translatable to injuries involving primarily diffuse axonal injury. The relationship between PTA duration and outcome in patients with predominantly focal pathology is less clear (34).

Two forms of secondary brain injury have been correlated with outcome, raised intracranial pressure and hypotension. Raised intracranial pressure has been shown to be a strong predictor of outcome per the Glasgow Outcome Scale (2,34,38). The effect of raised intracranial pressure on neuropsychological function is less clear. Both initial and maximum intracranial pressure have prognostic significance, however, maximum intracranial pressure better predicts outcome (39). The impact of intracranial pressure on outcome is unrelated to the age of the survivor, the GCS scores or the type of CNS lesion. Hypotension is perhaps the secondary brain injury most detrimental to survival and functional outcome. Hypotension, along with age, intracranial lesion, pupillary reactivity and post-resuscitation GCS score, is considered as one of the five most powerful predictors of outcome during the injury through resuscitation period (2). The presence of hypotension with systolic pressures of less than 90 mmHg or a cerebral perfusion pressure less than 70 mmHg at the time of resuscitation increases the mortality and significantly decreases functional outcome (40–43). In contrast hypoxia, although more prevalent than hypotension at resuscitation, results in only a slight increase in mortality and may have little impact on long term outcome (40).

Increasingly, studies have explored the relationship between impairments and extent of disability at the time of presentation to rehabilitation with functional outcome. One study looked at CT scan abnormalities present at the time of admission to acute rehabilitation; an association was noted with functional outcome and disposition at discharge from rehabilitation (44). Normal CT scans implied an 83% chance of achieving independent living skills, independent mobility and returning to home. On the other hand, large ventricles implied a very poor prognosis for independence in self-care skills and mobility. Only half of the latter patients were able to return to home (44). In addition, FIM scores at the time of initiating rehabilitation have been found to be useful predictors of discharge FIM score and rehabilitation length of stay (6). Similarly, FIM scores have been highly predictive of minutes of required assistance and the extent of supervision needs (45). The impairments that have a significant impact on FIM gain and efficiency are varied but include cognition, balance and medical comorbidities (15,16,21,46).

In summary, traumatic brain injury outcome is too complicated to be predicted accurately with one or several variables. Also, this literature is limited in that the overwhelming preponderance of studies exploring the

impact of premorbid, acute injury and post-injury indicators on functional outcome have utilized the Glasgow Outcome Scale as the primary outcome measure; the Glasgow Outcome Scale, however, provides limited information concerning functional skills and limited insight into the comprehensive cognitive, behavioral, and physical deficits common after a traumatic brain injury. Increasingly, studies are examining the prognostic information available at the time of presentation to rehabilitation. At this time, the strength of these predictors remains inadequate to dictate the rehabilitation programming needs of an individual. Hence, the increasing availability of good prognostic information assist the physiatrist in developing an appropriate comprehensive rehabilitation plan, but the data to date remain inadequate to supersede clinical judgment.

### **Early Rehabilitation Intervention**

The significance of early and more aggressive rehabilitation on improving functional outcome has been supported through the observations that prolonged acute care length of stay and a subsequent delay in the onset of multidisciplinary rehabilitation is associated with a longer rehabilitation hospitalization and lower functional outcome (7,47,48). However, functional outcome between the early admission and the late admission groups appears comparable at 2 years (47). These observations, however, cannot exclude the impact of other TBI comorbidities on observed outcomes. Another study examined early intervention on a neurotrauma service while the patient was still on a ventilator (49). Early intervention resulted in shorter rehabilitation stays, higher Rancho levels at discharge from rehabilitation, improvement in the percentage of subsequent patients requiring institutional placement after acute rehabilitation and perhaps most remarkably, shorter durations of coma. Similarly, studies have found that earlier psychiatric involvement after TBI is associated with better functional outcome presumably due to the subsequent earlier initiation of multidisciplinary rehabilitation interventions (50). Studies such as these are of enormous significance because the role of rehabilitation in decreasing impairments, disability and handicap while also decreasing long-term health care expenditures has never been directly proven. These studies, however, are part of a growing body of evidence that support the important role of early rehabilitation intervention.

### **Management of the Minimally Responsive Patient**

Definable stages of recovery have been reported for patients emerging from traumatic coma. These stages have been most lucidly outlined by Hagen, Malkmus and

**TABLE 19-2**  
**Rancho Los Amigos Levels of Cognitive Functioning**

I. No response
II. Generalized response
III. Localized response
IV. Confused – agitated
V. Confused – inappropriate
VI. Confused – appropriate
VII. Automatic – appropriate
VIII. Purposeful – appropriate

Durham who developed the Rancho Los Amigos Scale of Cognitive Functioning (Table 19-2) (51).

This scale uses behavioral observation to categorize a patient's level of cognitive functioning; it works well as a simple means by which clinicians can communicate an individual's level of cognitive functioning and develop appropriate rehabilitation strategies.

The initial three Rancho stages represent the low level, or minimally responsive, brain injury survivor. A patient emerging into Level III begins to demonstrate localized responses such as tracking, pulling tubes, restlessness and the beginning of command following. Responses initially are inconsistent, and become more reliable as the patient progresses through stage IV. Recovery through Rancho Levels I, II and III may be protracted in one of eight severe TBI survivors (52). Therefore, objective means to document progress, monitor cognitive status and determine the therapeutic efficacy of intervention becomes an important adjunct in the clinical management of vegetative or low level, coma emerging populations. Examples of two scales utilized for the monitoring of vegetative or low functioning, coma emerging survivors are the Western Neurosensory Stimulation Profile and the Coma/Near Coma Scale.

The Coma/Near Coma Scale consists of eight parameters each with a specified number of stimuli and trials (53). Based on the numerical scoring system, patients are stratified into 1 of 5 categories: no coma, near coma, moderate coma, marked coma and extreme coma. The Coma/Near Coma Scale can be administered quickly. The Western Neuro Sensory Stimulation Profile is a more extensive instrument that consists of 32 items that assess arousal, attention, response to stimuli and expressive communication (54). This instrument, however, requires 20–40 minutes to complete. Both instruments have good interrater reliability and documented construct validity. However, the literature describing the utility of these or other instruments for monitoring the clinical course of vegetative or coma emerging patients remains limited.

Coma rehabilitation, or multisensory stimulation programs are rehabilitation programs designed for patients

that are in coma, coma emerging or a vegetative state that have as a primary purpose the prevention of complications associated with prolonged immobilization and the creation of an environment in which the patient has the maximum chance to emerge. This is accomplished by means of a multidisciplinary program involving medical and nursing interventions, sensory stimulation, regular exercise and family education (55,56). It is believed that in this environment, central nervous system pathways will begin to be able to process information with increasing complexity. Advocates of these programs profess that their intervention potentiates the maximum chance of recovery, allows close monitoring of cortical function and facilitates the development of the best overall care plan for the patient. However, a recent review of sensory stimulation literature for brain injured patients could find no adequate clinical trials or evidence to support, or for that matter, rule out the effectiveness of multisensory programs for patients in coma or vegetative states (56).

Multisensory stimulation programs typically stimulate the five senses directly and the patient responses are assessed with the intent of advancing the stimulations as the complexity of response increases (55). However, the optimal nature and frequency of stimulation remains to be defined and varies considerably through the literature. Programs range in intensity between two sessions of 10 minutes each per day to 36 repetitions of the sensory stimulation procedure per day, 7 days per week (55–58). In addition to the lack of consensus as to the nature of the intervention program, interpretation of the available literature suffers from a lack of consistency in definitions of coma or the vegetative state (56). Frequently, the outcome measures were either not objective or lacked clinical significance. These methodologic issues lead one to conclude that there is no compelling evidence to support or refute the possibility that the multisensory stimulation interventions are more effective than standard multidisciplinary rehabilitation at arousing the patient from coma or reducing the time to recover from coma (56). However, in view of the medical, psychological, economic and social implications associated with the treatment of this population, well designed investigation of multisensory stimulation after brain injury is warranted to determine if this strategy should be incorporated as a standard of care.

### Post-Traumatic Amnesia

Post-traumatic amnesia (PTA) represents a form of delirium that is both unique to traumatic brain injury survivors and universal in that all survivors of moderate and severe TBI experience post-traumatic amnesia. The period of post-traumatic amnesia has considerable clinical significance. Prognostic information can be discerned from this stage of recovery and both the cognitive and behavioral characteristics of post-traumatic amnesia have



an immediate impact on rehabilitation intervention strategies.

The definition of post-traumatic amnesia has evolved over time. Initially it was described by Russell as indicating a period of impaired consciousness after head injury (59). Later post-traumatic amnesia was defined as “taken to end at the time from which the patient can give a clear and consecutive account of what was happening around him” (60). Others have described post-traumatic amnesia as an absence of continuous memory or an inability to retain new information. Today, post-traumatic amnesia suggests the broader syndrome of disorientation to time, place and person, confusion, diminished memory and reduced capabilities for attending and responding to environmental cues (61).

Symonds in 1928 was the first to identify length of coma as an estimate of prognosis after brain injury (62). In 1882, Ribot proposed a classification of amnesia that included both anterograde and retrograde amnesias (63). The concept and clinical significance of post-traumatic amnesia, however, was first suggested in 1932 by Russell (59). Retrograde amnesia implies an inability to retrieve information that was acquired prior to the onset of a specific pathologic event (64). Typically retrograde amnesia involves a gradient; events closer to the injury are less likely to be recalled than earlier memories occurring before the injury. As the patient improves and confusion clears, the duration of retrograde amnesia usually shrinks from perhaps years to approximately 30 minutes or so preceding the pathologic event. After the survivor clears post-traumatic amnesia, the retrieval of remote memory remains impaired but there is no longer a temporal gradient; that is, there is not selective sparing of the oldest memories (64,65). Retrograde amnesia is rarely an isolated event and typically, post-traumatic amnesia is significantly longer than the duration of retrograde amnesia (66).

Post-traumatic amnesia is rarely if ever complete (67). Levin, et al found that during post-traumatic amnesia, initial learning and accelerated forgetting are both problematic but forgetting is particularly accelerated whereas acquisition of new information is less impaired (68). Also, patients during post-traumatic amnesia can demonstrate long-term learning, especially involving tasks that require limited attention. For example, a patient may demonstrate learning during post-traumatic amnesia in situations where the probability of response is increased with repetition (69). A patient may also learn during post-traumatic amnesia through stimulus response training such as acquisition of motor skills (60). The concept of learning during post-traumatic amnesia is salient to the rehabilitation professional in that issues of self-care, mobility and locomotion can be successfully addressed during this amnesic stage. Similarly, problem behaviors can be addressed during this amnesic state with behavioral interventions that are consistent and repetitious.

The duration of post-traumatic amnesia is a marker of injury severity and carries significant prognostic implications. By 1961, the duration of post-traumatic amnesia was thought to represent “the best yardstick we have” of blunt head injury severity (70). Over the decades, it has been demonstrated that the length of post-traumatic amnesia is predictive of functional outcome, return to work, occurrence of post-traumatic epilepsy and cognitive recovery (19,22,71–79).

Predicting resolution of post-traumatic amnesia also carries significant therapeutic implications in that the resolution of post-traumatic amnesia is often associated with a marked improvement in behavior, a reduction in agitation, an improvement in attention, a readiness to tolerate the demands of a more comprehensive neuropsychological assessment, and an increase in capacity to more fully participate in a comprehensive rehabilitation program (80). Therefore, predicting whether and when a patient will clear post-traumatic amnesia is useful in establishing a survivor’s programming needs. It has been speculated that the duration of post-traumatic amnesia is approximately four times the duration of coma, but other studies have failed to support the length of coma as a reliable predictor of clearing post-traumatic amnesia (80,81). A younger age implies a greater likelihood of clearing post-traumatic amnesia but age does not accurately predict when the survivor will clear this stage. Finally, several attempts to predict post-traumatic amnesia duration early in the post-acute period utilizing validated instruments that prospectively measure post-traumatic amnesia duration have yielded mixed results. Specifically, time after trauma and the first weekly aggregate score assessed by the Orientation Group Monitoring System accounted for only 15.9% of the variance (80). However, a model utilizing the Modified Oxford PTA Scale found that a three variable regression model, consisting of day after trauma when testing was started, rate of change of post-traumatic amnesic scores over the first 5 days of testing and the score on the first day of testing accounts for 89% of the variance in observed length of post-traumatic amnesia (82).

Traditionally the duration of post-traumatic amnesia has been estimated retrospectively. This is potentially problematic in that islands of intact memory may develop when the patient otherwise is unable to sustain continuous memory (83,84). Therefore, retrospectively inquiring as to the time of the first intact memory post-injury could result in an underestimation of post-traumatic amnesia duration. Similarly, retrospectively inquiring as to the interval when orientation normalized can lead to a misleading estimate of post-traumatic duration; 10% to 20% of survivors may be oriented without having cleared post-traumatic amnesia (83,85).

The first instrument developed to prospectively assess the duration of post-traumatic was the Galveston Orientation and Amnesia Test (GOAT) (84). This instrument is

**TABLE 19-3**  
*Prospective Measures of Post-Traumatic Amnesia Duration*

Galveston Orientation and Amnesia Test (68)
Oxford PTA Scale (25)
Orientation Group Monitoring System
Westmead PTA Scale (91)
Julia Farr Services PTA Scale (92)
Modified Oxford PTA Scale (24)

reliable (Kendall Correlation Co-efficient of 0.99). The core application for this instrument is the assessment of temporal orientation. This instrument can be administered daily at bedside during the course of a brief interview. Construct validity for the GOAT has been demonstrated through correlation with Glasgow Outcome Scale level, the severity of computed tomography findings, and functional outcome. Finally, the GOAT's brevity renders it more applicable to monitor recovery through PTA in the acute care setting than the other more extensive assessments of PTA such as the Orientation Group Monitoring System (86–89). Other instruments have subsequently been developed to prospectively measure the duration of post-traumatic amnesia (Table 19-3) (90–92).

Each instrument emphasizes different constructs of post-traumatic amnesia, and with the exception of the Orientation Group Monitoring System, are generally brief, lending themselves to bedside utilization. The Orientation Group Monitoring System is based on behavioral observations during a scheduled therapeutic orientation group and, therefore, is appropriate for an inpatient rehabilitation setting where its utility in the early detection of evolving medical complications that present as a decline in cognitive function can be utilized (89). The Galveston Orientation and Amnesia Test is the most widely utilized prospective assessment of post-traumatic amnesia with well established, sound psychometric properties (93).

Thus, the period of post-traumatic amnesia has important clinical significance. The duration of PTA carries prognostic implications concerning long-term outcome. During PTA, acquisition and storage of memory are impaired but under proper circumstances, new functional skills can be acquired. Finally, the behavioral and cognitive abnormalities characteristic of PTA carry significant therapeutic implications regarding supervision needs and formalized programming needs.

### **Agitation**

Perhaps the most compelling behavioral change during post-traumatic amnesia is post-traumatic agitation. Denny-Brown (1945) first described restlessness as a

natural sequela of traumatic brain injury (94). The classic example of agitation is the patient at Level IV of the Rancho Los Amigos Level of Functioning who is “confused-agitated” and functioning in a heightened state of activity and diminished capability for processing new information or responding to events in the environment. Various estimates of agitation incidence have ranged between 11%, 33% to over 50% (95,96). In part, this disparity was related to the absence of a consistent definition. In 1996, Sandel and Mysiw defined post-traumatic agitation as a subtype of delirium unique to TBI patients who are still in post-traumatic amnesia and who demonstrate excesses of behavior that include akathisia, aggression and emotional lability (97). This definition is consistent with the constructs defined in both the Agitated Behavior Scale, a reliable and valid instrument, designed to measure the severity and nature of post-traumatic agitation (98), and a survey of expert TBI rehabilitation psychiatrists (99).

The initial approach to the agitated patient includes a comprehensive examination emphasizing other medical or neurologic etiologies for the observed behavior prior to initiating treatment strategies. Fractures, peripheral nerve injuries, skin lesions, J/G-tube sites and tracheotomy sites, for example, are potential sources of noxious stimuli that left untreated with appropriate analgesia may present as agitated behavior in the coma emerging, confused patient. In addition, all medical conditions that have the potential to result in a decline in mental status or cognitive function should be considered as studies have shown that cognition improves before agitation and a decline in cognition often results in an increase in agitation (15,100). Also, all pharmacologic interventions should be reviewed for evidence of toxicity or adverse reactions.

Management strategies utilized in treating agitated behavior include one-to-one monitoring, behavioral modification, physical restraints, environmental modification and pharmacologic intervention (101). As rehabilitation stays shorten, the prompt resolution of agitation becomes increasingly important so as to not interfere with other treatment goals (101). Therefore, pharmacologic intervention has also become increasingly important as an adjunct in the treatment of the agitated traumatic brain injury survivor.

There have been six randomized clinical trials published exploring pharmacologic treatment options for agitated aggressive behavior after brain injury (102–107). Four of these studies looked at the role of beta blockers, one studied methylphenidate and the sixth study utilized amantadine. The beta blockers did appear to be most effective, but the population studied was not limited to traumatic brain injury survivors. The methylphenidate study looked at an aspect of agitation, namely aggression, in a group of TBI survivors who cleared post-traumatic amnesia. The amantadine study utilized a behavioral outcome not ideally suited to the assessment of post-traumatic agitation.

The balance of the studies exploring the efficacy of pharmacologic interventions for post-traumatic agitation are primarily case reports or series that utilized an AB rather than ABA design and lacked a reliable outcome measure. Also, these studies fail to consider the impact of the pharmacologic intervention on outcome. As previously noted in the post-stroke population, evidence has begun to emerge that suggests that certain categories of pharmacologic agents utilized in the acute care setting, namely neuroleptics, do have a negative impact on cognitive recovery during the rehabilitation setting (108).

Several classes of medications are most commonly utilized in the management of post-traumatic agitation (Table 19-4).

A survey of the American Academy of Physical Medicine and Rehabilitation Brain Injury Special Interest Group in 1997 revealed that the five most frequently prescribed drugs to diminish the severity of post-traumatic agitation were carbamazepine, tricyclic antidepressants, trazodone, amantadine and beta-blockers (99). During episodes of extreme agitation, the literature appears to support abortive agents such as short-acting benzodiazepines or atypical antipsychotics (109).

Data suggest that as patients emerge from coma, improvement in cognition precedes resolution of agitation (15,87). This supports the clinical observation that agitation management strategies that diminish cognition may, in fact, prolong and exacerbate agitation. Therefore, the ideal pharmacologic management of post-traumatic agitation would include the simultaneous objective monitoring of both the agitation severity and cognitive function. The Agitated Behavior Scale has been validated to provide an assessment of agitation severity, duration and the relative contribution of aggression, disinhibition or lability to the observed behavior (98). Two instruments that lend themselves to monitoring cognitive recovery during pharmacologic intervention of agitation include the previously mentioned Galveston Orientation and Amnesia Test and the Orientation Group Monitoring System (84,86). In the rehabilitation setting, the Orientation Group Monitoring System does offer a distinct advantage over the GOAT

through its increased sensitivity in detecting medical complications such as adverse drug effects, infections and hydrocephalus (88). The GOAT's brevity renders it the more useful instrument in the acute care setting.

In summary, multiple pharmacologic treatments have been proposed for the management of post-traumatic agitation; the efficacy and indications remain largely unproven. The optimal medication would: 1) control behavior without sedation; 2) augment or at least not delay or interfere with recovery of cognition; and 3) maintain a low side-effects profile. Given the heterogeneity of primary and secondary brain injury mechanisms, injury severity, presence of pre-existing conditions and the variable clinical presentation of post-traumatic agitation, it is unlikely that one pharmacologic agent will evolve as effective in the management of agitation in all or even a majority of survivors.

### Cardiovascular Autonomic Disorders

Cardiovascular disorders associated with TBI may include rhythm disturbances, ischemic changes, cardiac contusion, hypotension and hypertension. Of these, hypertension is the most common and immediate cardiovascular disorder associated with severe head injury (110). In fact, autonomic dysfunction has been reported in 15–33% of acute brain injury survivors (111,112). The condition is most commonly found after brainstem or diffuse axonal injury. Although tachycardia, fever and hypertension represent the most frequent presenting signs, the physical findings could include any combination of autonomic disturbances. (Table 19-5).

This diagnosis of autonomic dysfunction is a diagnosis of exclusion (Table 19-6) (111,112).

In the event that the clinical picture primarily involves hypertension, then other etiologies can be considered such as increased intracranial pressure (113), hydrocephalus (114), or medications such as steroids or nonsteroidal anti-inflammatory drugs.

The presence of autonomic dysfunction is associated with morbidity, due to possible secondary myocardial infarction, intracerebral hemorrhage, rhabdomyolysis. The hypertension and associated medical instability may

**TABLE 19-4**

*Classes of Medications Commonly Used to Treat Post-Traumatic Agitation*

- Benzodiazepines
- Anticonvulsant
- Antidepressant
- Antipsychotics
- Buspirone
- Amantadine
- Beta-blockers
- Lithium

**TABLE 19-5**

*Common Presentations of Autonomic Dysfunction After Brain Trauma*

- Hypertension that is either constant or fluctuating
- Fever that may range from low grade to high
- Tachycardia
- Pupillary dilation
- Diaphoresis
- Dystonia or extensor posturing

**TABLE 19-6**  
**Differential Diagnosis of Autonomic Dysfunction**  
**After Brain Trauma**

- Infection/sepsis
- Neuroleptic malignant syndrome
- Autonomic dysreflexia secondary to spinal cord injury
- Malignant hyperthermia
- Pheochromocytoma
- Thyroid storm
- Delirium tremens
- Lethal catatonia
- Serotonin syndrome

preclude initiation of most direct rehabilitative interventions. As such, patients who experience autonomic dysfunction are likely to require longer periods of inpatient rehabilitation and tend to have a longer period of post-traumatic amnesia, poorer Glasgow Outcome Scale score and lower Function Independence Measure score.

Again, although autonomic dysfunction is seen in 15–28% of TBI survivors acutely in the rehabilitation setting, the incidence is estimated to be between 10 and 15% and the prevalence diminishes rapidly to less than 3% after discharge (110,115). In Labi and Horn's retrospective study of 74 patients with no premorbid history of hypertension who were discharged from a rehabilitation hospital after their first TBI, only 11 (15%) developed hypertension during admission (115). Five (7%) were discharged on anti-hypertension medication, of whom 3 were able to discontinue or reduce medication at 1 month after discharge and 2 were lost to follow-up. In the interim, the treatment involves controlling the blood pressure with beta blockers or alpha blockers (116). In the more advanced forms of autonomic dysfunction, spasmolytics such as dantrolene, and analgesics such as opiates and either dopamine agonists or antagonists may prove effective at ameliorating some of these symptoms (117).

Hypotension in the rehabilitation setting is frequently associated with prolonged bed rest or medication adverse effects, volume depletion or neuroendocrine abnormalities. The most common medications causing orthostatic hypotension are anti-hypertensive, in particular diuretics, alpha blockers and vasodilators.

Electrocardiographic abnormalities commonly accompany early recovery from TBI. Incidence after severe head injury varies from greater than 80% during the acute medical admission (118) to approximately 20% during inpatient rehabilitation (110). ECG evidence suggesting myocardial ischemia, including prolonged QT interval, inverted T waves, and ST segment elevation has been well documented in the neurosurgical literature (113,118,119). Myocardial injury has been corroborated through

laboratory medicine and at autopsy. CK-MB activity may remain elevated at least 3 days after injury (113). Histologic evidence of myocardial necrosis at autopsy has confirmed the presence of myocardial injury following head injury (120). In the absence of direct cardiac trauma, myocardial damage may be secondary to massive release of catecholamine from autonomic dysfunction (121).

Dysrhythmias appear to occur less commonly, although the incidence has not been studied after TBI. Case reports include life-threatening torsades de pointes, concomitant pulsus alternans and U-wave alternans, transient heart block ranging from prolonged PR intervals to high-grade AV block with ventricular escape rhythm (121–124). Most commonly seen in the rehabilitation setting are nonspecific ST and T wave changes (110). Given the potential for underlying myocardial damage, baseline EKG at the time of rehabilitation admission is a valuable screening exam and an important adjunct to a thoughtful cardiopulmonary evaluation.

### Respiratory Disorders

Respiratory or pulmonary complications noted after traumatic brain injury include those directly related to trauma such as pneumothorax, hemothorax and flail chest. In addition, a number of pulmonary complications occur that are at least, in part, related to the subsequent neurologic dysfunction, including: respiratory failure, pneumonia, neurogenic pulmonary edema and tracheal/airway complications (125). Pulmonary complications are the most frequent complications occurring after the acute trauma through the rehabilitation hospital stay, with up to 60% of patients experiencing pneumonia, respiratory failure occurring in up to 43% and 39% requiring a tracheotomy (16,125–132).

In a British analysis of mortality after pediatric TBI, 93% of potentially preventable deaths prior to hospital admission were of respiratory etiology, predominantly aspiration (133). Following admission one quarter of all deaths were attributable to pulmonary abnormalities. Of those considered to be preventable deaths, nearly 60% were secondary to respiratory arrest or airway obstruction. More recent data has documented that the presence of respiratory failure, pneumonia and tracheotomies show a strong relationship to both acute and inpatient rehabilitation length of stay (16). In addition, those survivors without respiratory failure or who did not require a tracheotomy demonstrated a better one year outcome per the Disability Rating Scale and the Function Independence Measure (16).

Alcohol intoxication, frequently associated with TBI, is a significant risk factor for respiratory complications. In a study of 520 patients, nearly 40% were intoxicated at the time of admission (134). Although injury severity appeared similar to the non-intoxicated cohort, intoxicated patients were 30% more likely to require

intubation prior to admission and 80% more likely to have respiratory distress requiring artificial ventilation during the acute care admission. Potential factors contributing to a 40% greater risk of pneumonia included ethanol related immune suppression, a higher likelihood of aspiration and/or a higher prevalence of pneumonia preceding the TBI. Of note, where alcohol intoxication was documented on admission, length of hospital stay was not extended unless pulmonary complications developed, specifically respiratory distress or pneumonia. Given the frequency of these complications, alcohol intoxication complicating TBI has obvious economic and public health ramifications.

The majority of patients who undergo tracheotomy will recover sufficient neurologic integrity to consider decannulation. Decannulation is pursued when the individual no longer requires ventilation, effectively manages their secretions and is thought to be at low risk for aspiration (125). There is no standardized protocol for decannulation. Usually this is accomplished in a stepwise fashion with incrementally decreasing the cannula diameter followed by a trial of plugging the tube; if the patient is asymptomatic, has an effective cough and manages their secretions, then the tube is finally removed and an occlusive dressing is applied (125). Prospective studies of patients with long term tracheotomy, using direct laryngeal visualization prior to decannulation have demonstrated an incidence of serious abnormalities which exceeds 30%, in both the acute and subacute setting (129–131). Tracheal stenosis, subglottic stenosis, glottic stenosis, tracheomalacia, tracheal granuloma are seen most frequently with varying degrees of clinical symptoms. In view of these complications, direct laryngoscopy prior to decannulation has been suggested.

Where studies have stratified by cognitive level, as expected, morbidity and mortality are much higher for decannulation at Rancho Levels II and III (129). Central respiratory lability and poor pulmonary toilet with resultant pneumonia leading to sepsis contribute significantly to the increased mortality in the vegetative and coma emerging patient. Hence, the appropriateness or merit of decannulating patients who remain severely neurologically compromised remains uncertain. On the other hand, predictors of successful decannulation include: 1) traumatic mechanism of brain injury; 2) younger age; and 3) alert cognitive status (130). Also, of those in whom adequate cough and swallowing reflexes have been documented, complications are not observed to correlate with age, diagnosis, Rancho scale or duration of tracheotomy (131).

Several factors may predispose to increasing laryngotracheal mucosal reaction following traumatic brain injury (129). Emergent intubation frequently occurs under less than optimal circumstances. The peri-injury and acute stabilization period are frequently complicated by hypotension and resultant tissue hypoxia (129). Cervical

hyperextension associated with decerebrate or decorticate posturing can enable the posterior pharyngeal tissues to act a fulcrum for the rigid endotracheal tube (132). Head movement, potentially creating a see-sawing movement of the tube, may be marked with agitation (132).

Prolonged tracheal intubation is known to result in a number of complications. These complications can be diminished with proper choice of tube, meticulous attention to details of airway management to prevent excessive movement of the tube during turning, suctioning, and ventilator connection/disconnection, adequate sedation to prevent coughing, agitation and decerebrate or decorticate posturing, adequate humidification, use of soft nasogastric tubes, and prevention of tissue hypoxia, anemia and infection all of which further increase the risk of tissue injury.

### Fever

A common acute complication after a severe traumatic brain injury is fever. Although frank fever of unknown origin (temperature elevation of greater than 38.2° C on several occasions over at least a 3 week period of time and an inability to diagnose the underlying etiology after at least 1 week of intensive investigation) (134) is unusual, a similar systematic approach to diagnose the underlying etiology is often warranted. The differential diagnosis for fever of unknown origin is extensive and includes infectious, neoplastic, autoimmune, granulomatosis, metabolic, inherited, psychogenic, periodic and thermoregulatory disorders (134). The list of likely sources of fever after a severe traumatic brain injury is less extensive but this framework is often useful for accurate diagnosis (135).

Urinary tract infections affect approximately 40% of traumatic brain injury survivors during the rehabilitation phase of recovery (110). Ureteral obstruction is seen in approximately 1% of patients after a traumatic brain injury. Other potential genitourinary sources of fever include pyelonephritis, perinephric abscess and prostatic abscess.

Approximately 34% of traumatic brain injury survivors develop respiratory complications that predispose them to pulmonary infections (110). Poor ventilation with secondary atelectasis is thought to be the most common pulmonary complication of trauma and a potential forerunner of pneumonia. Tissue necrosis secondary to lung trauma with subsequent formation of a pulmonary cavity may also predispose the patient to secondary lung infections (136). The presence of endotracheal or tracheotomy tubes predispose patients to bacterial colonization and a greater risk of secondary lung infection. Finally, tubes utilized for enteral feeding increase the probability of aspiration pneumonia by as much as 25%.

The head and neck area includes several other potential sources of fever after a traumatic brain injury.

For example, perinasal sinusitis after nasotracheal intubation has been estimated to occur in approximately 26% of patients (139,140). Also nasogastric intubation has been reported to cause a similar rate of sinusitis and fever in trauma survivors. Finally, within the head and neck area, dental abscess is a potential etiology secondary to teeth rendered non-viable by trauma (141).

Cardiovascular etiologies for fever include subacute and acute endocarditis (142), dissecting aortic aneurysm (143), intravenous line sepsis (144) and thromboembolic disease (145). The incidence of thromboembolic disease after traumatic brain injury has been reported to occur at a rate as low as 4% during the rehabilitation course. However, this incidence is possibly low due to the nonspecific clinical presentation of thromboembolic disorders and the concomitant issue of impaired arousal and cognition.

Other sources for fever include musculoskeletal etiologies such as heterotopic ossification, (146) which can mimic deep venous thrombosis in its presentation, and osteomyelitis from either hematogenous or contiguous spread (110). Perisplenic, pericardial and retroperitoneal cryptic hematomas have been associated with a prolonged fever after trauma (110,147). Adverse reactions to medications includes drug fever; an important and potentially life threatening example of this would be the neuroleptic malignant syndrome (148,149). Finally, neurologic etiologies for fever after trauma would include bacterial meningitis, infected intraventricular shunts, hyperthermia reactions to acute hydrocephalus, neurogenic hyperthermia and the post-ictal period (150–154).

### **Bladder and Bowel Function**

Traumatic brain injury often results in injury to the frontal lobes resulting in loss of cortical control over urination and defecation (155). In addition, injury to the subcortical structures can result in the development of bladder dysnergia. In one large study of brain injury survivors, 38% of patients developed urinary tract infections. Although the majority of these patients had indwelling Foley catheters, 37% did not. Therefore, bladder dysfunction was seen in 8% of the cohort (110).

The incidence of urinary incontinence during the first 6 weeks after TBI has been found in approximately 62% of patients (156). Also, 9.5% of survivors are found to have evidence of urinary retention (156). Urodynamic studies primarily document an uninhibited over active bladder where the patient demonstrates loss of voluntary control over micturation, disturbed bladder perception and poor sphincter control to the extent that upon virtually the first sensation of filling, the patient develops almost immediate micturation (157).

The clinical significance of urinary incontinence and retention early in the coma emerging brain injured patient is that this increases the risk of urinary tract infection and

the development of skin ulcer (156,157). Also, the presence of urinary incontinence is associated with a poorer functional outcome at discharge from both acute care and inpatient rehabilitation and it increases the likelihood of requiring a long-term care disposition (156).

Treatment options for urinary incontinence after TBI includes behavioral strategies such as a timed voiding program (158). All predisposing factors to urinary tract infections such as Foley catheters, bladder retention, fecal incontinence, and inadequate hydration, are removed or addressed. A timed voiding program initially begins with toileting the patient frequently with gradual increases in interval length. For the patient who voids frequently in small amounts with low post-void residual volumes, anti-cholinergic agents can be considered as an adjunct (159). However, important possible adverse effects of anti-cholinergic agents include a slowing of cognitive recovery, worsening of delirium and the development of urinary retention.

Bowel dysfunction after traumatic brain injury often results from a loss of cortical control over the defecation reflex causing the patient to be incontinent. In addition, constipation is a frequent occurrence in the acute care setting due to lack of mobility, use of potentially constipating medication and alteration in normal diet. Stool softeners, osmotic laxatives, stimulant suppositories and adequate hydration are often helpful initially to maintain bowel regularity. As the patient recovers, the bowel program should be tailored to additionally utilize the gastrocolic reflex, approximately 30 minutes after eating, as well as gravity by having them sit in an upright position to defecate. As noted with urinary incontinence, the presence of bowel incontinence is associated with a more severe injury and poorer functional status at both acute care and other inpatient rehabilitation (160).

Diarrhea is a common occurrence in low level brain injury patients on enteral feedings. This can lead to loss of skin integrity, infect pressure sores and other wounds, and result in severe dehydration. Use of formulas high in fiber, and using isosmotic formulas are often helpful. Supplementing the enteral feeding with fiber compounds such as psyllium mucilloid can also be helpful in forming stool. The use of anti-diarrheal medications are not necessary and in the case of loperamide can be potentially sedating. Patients after severe traumatic brain injury often require antibiotic treatment for various infections, are debilitated, and in the hospital; thus they are at significant risk for the development of bowel infections. In the patient who has persistent diarrhea, infectious etiology should be considered (139).

### **Swallowing and Nutrition**

Two primary nutritional issues confront the TBI survivor, the timing of initiating nutritional support and the optimal

route of administration. After moderate or severe TBI, the patients demonstrate and increase in caloric requirements (161) due to hyper metabolism, increased energy expenditure and increased protein loss (162–164). This state can persist for up to 4 weeks (121). Studies have shown that early nutritional support prevents the loss of immune competence, decreases morbidity and mortality, shortens the length of hospital stay and may decrease subsequent disability (165–168).

The merits of enteral (gastrostomy versus jejunostomy) versus parenteral routes of nutritional support are not resolved. As arousal improves, swallowing evaluations involving a combination of bedside swallowing assessments or video fluoroscopy, are performed by a speech-language pathologist or occupational therapist, are warranted as swallowing disorders are estimated to occur in 25–30% of brain injury survivors (169,170). The video fluoroscopic evaluation is often an essential adjunct in the evaluation of these patients because physical findings alone are not sufficiently sensitive to predict the ability to safely swallow. In a study by Winstein, (170) 12% of patients with swallowing disorders had normal gag reflexes and 77% has a good voluntary cough reflex. Thus, the information provided by a comprehensive assessment helps the clinician to make important judgments about the patient's ability to begin oral feeding and which swallowing strategies would most facilitate safe swallowing.

At first, oral feeding is often restricted to therapeutic purposes and requires the direct supervision and intervention by a speech-language pathologist or occupational therapist. Safe therapeutic feeding is additionally predicated on the survivor's behavioral sequelae; behaviors such as agitation, impulsivity, lack of initiation, and hyperphagia should be monitored for and, when present, treated using appropriate behavioral management interventions. After oral feeding has begun, it is sometimes difficult for the patient to maintain adequate caloric intake necessitating a combination of oral and enteral feeding and close monitoring of nutritional status. Attempts to advance oral feeding are intermittently slowed by the loss of appetite. In these instances, a specific etiology should be sought such as an evaluation of taste and smell due to cranial nerve or cortical dysfunction, as well as local trauma, leading to anosmia and/or gustatory dysfunction. Depression, neuroendocrine perturbations and pharmacologic interventions should also be considered as etiologies for decreased appetite.

### **Spasticity, Dystonia and Other Muscle Overactivity**

After a traumatic brain injury, spasticity, dystonia and other forms of muscle overactivity are not limited to the limbs but can also present in the torsal, facial, and oral pharyngeal musculature. Interventions are clearly

warranted when the muscle tone significantly interferes with achievement of rehabilitation goals. Otherwise, it is a commonly held tenet that spasticity should not be treated unless it interferes with function. However, the veracity of this approach in a coma emerging patient, where plasticity may be affected by the consequence of abnormal tone has not been adequately studied.

The first stage of treatment for spasticity involves physical modalities, range of motion, and exercise.

Cryotherapy has been found to be helpful in temporarily reducing spasticity for 1 to 3 hours after application (171). This is often sufficient time to allow for therapeutic interventions including serial casting, ambulation or range of motion exercises. Application of casts to preserve or increase range of motion has been shown to have a secondary beneficial affect on reducing spasticity (172). Thus, through the use of serial casting early in the care of brain injury patients, improvements in tone and maintenance of joint range of motion can be fostered.

If spasticity continues despite these interventions, pharmacologic therapy is indicated (173,174). Unfortunately, the use of anti-spasticity medications can have negative effects on cognition (88). In the traumatic brain injury population, dantrolene sodium becomes an attractive pharmacologic agent, primarily because of low potential for cognitive side-effects; however, routine blood monitoring is required because of potential toxic effects on the liver. Other anti-spasticity medications primarily include tizanidine, baclofen and the benzodiazepines; a wide variety of other off-label agents exist with some value in tone reduction (173,174). Although these medications can all help with tone reduction, they require close monitoring because of the significant potential for impairing cognition.

If pharmacotherapeutic interventions are ineffective in reducing spasticity, motor point blocks, nerve blocks and botulinum toxin are effective in reducing tone in a specific group of muscles such as lower limb adductors or plantar flexors. Neurectomies and intrathecal infusion of baclofen have been shown to help with persistent hypertonicity (177,178). However, during the early rehabilitation assessment and intervention after TBI, these more invasive interventions are rarely indicated.

## **TERTIARY PREVENTION**

### **Venous Thromboembolism**

Deep venous thrombosis (DVT) represents a significant source of morbidity and potential mortality for patients with head trauma. Pulmonary embolism from DVT is apparently increasing in importance as a cause of death of inpatients with traumatic brain injury (179). The NIH Consensus Conference estimated the incidence of DVT after severe traumatic brain injury to be approximately

40% and the incidence of fatal pulmonary embolus is approximately 1% (180). The incidence of DVT in TBI patients upon admission to inpatient rehabilitation has been estimated as high as 20% (181,182). Despite these data, there is no standard of care for DVT prophylaxis, screening or treatment after TBI. In part, this is secondary to the safety concerns associated with the use of anticoagulation after trauma and a traumatic brain injury. However, there is increasing evidence to support the safety of initiating either heparin or low molecular weight heparin (LMWH) within 24–72 hours of severe head injury or intracranial bleed (183,184). Similarly, the value of screening for DVT at presentation to inpatient rehabilitation has been supported (185). The incidence of DVT can be significantly reduced using a specialized approach of prophylactic intervention in conjunction with routine monitoring in high risk patients. High risk categories include: 1) advanced age; 2) severe injury; 3) prolonged immobilization; 4) number of transfusions; 5) presence of clotting disorder (179,186–190).

In the event that prophylaxis against DVT is initiated, The Eastern Association for the Surgery of Trauma Practice Guidelines for the Prevention of Venous Thromboembolism in Trauma Patients in 2002 suggested that pneumatic compression devices may be of some benefit, LMWH is superior to heparin for prophylaxis in moderate to high risk trauma patients and duplex ultrasound is appropriate to diagnose symptomatic DVT and may be appropriate for screening of high risk asymptomatic patients (191). In those patients who are unable to receive these forms of prophylaxis, prophylactic Greenfield filter placement deserves strong consideration.

### **Contractures**

Contractures of the limbs, as well as the axial skeleton can potentially have devastating implications on self-care, mobility and even vocalization. Persons who are at greatest risk for contractures are those with: 1) a long period of coma and immobilization; 2) severe brain injury; and 3) altered muscle tone. The best treatment of joint contractures is prevention of contractures by an ongoing program of range of motion exercises and maintenance of postural adaptation (i.e., sitting, lying prone or supine and standing). Serial casting has been shown to be useful in the prevention and treatment of contractures (172,192,193). The therapeutic benefit of continual casting versus casting/bi-valve splinting has been debated with the current literature suggesting that continuous casting has a slightly better therapeutic advantage (193). However, others question the therapeutic value of orthotics and actively discourage their utilization due to a concern that motor relearning may be affected (194).

Once contractures develop, treatment depends on the severity of the contractures. Treatment options

include an aggressive stretching program in association with physical modalities, serial casting, and dynamic bracing. Pharmacologic interventions are initiated to address abnormal muscle tone. Other more focal interventions such as botulinum toxin, motor point blocks or neural blocks may be adequate and, thereby, minimize the potential adverse cognitive effects of antispasticity medications. In extreme cases, surgical release of the contracted tissue may be warranted to increase function. Surgical release of contracted tissue can improve skin care and hygiene, prevent the development and foster the healing of pressure sores, reduce pain and improve transfers and ambulation (186). However, such aggressive intervention for contractures is limited to the more chronic survivor who has failed conservative measures and are rarely if ever considered in the early course of the coma-emerging patient.

### **Fractures**

The incidence of concurrent fractures in patients with traumatic brain injury is approximately 30% (195); approximately 11% of these fractures are initially undetected (196). In brain injury survivors with fractures, there is an associated high risk of developing heterotopic ossification (197). This occurs especially in patients with forearm (198) and hip fractures (195). In a cohort of patients with hip fractures after traumatic brain injury, 100% developed heterotopic ossification (187). Conventional treatment of fractures including splints and casting often results in less than desirable results. Uncontrolled limb motion is common in the brain injury survivor especially early in the recovery as the patient emerges from coma (195). Early definitive fixation of upper and lower limb fractures allows for a shorter period of immobilization, early range of motion activity and less overall nursing care (198). Early mobilization and range of motion activities reduces the likelihood of developing severe spasticity, contractures, and ankylosing heterotopic ossification. In addition, early definitive fixation diminishes the need for casting of limbs, which often interferes with rehabilitation intervention.

### **Peripheral Nerve Injuries**

It has been estimated that 34% of patients admitted to a rehabilitation unit were diagnosed with previously undetected peripheral nerve injuries (199). Ulnar nerve entrapment in the cubital tunnel was found most frequently with brachial plexus injury and common peroneal compression neuropathies of slightly less frequency (199). Median nerve compression at the wrist has been reported in brain injury patients with wrist and finger flexor spasticity (200). Factors that are felt to contribute to compression neuropathies in the brain injury population include: 1) extrinsic pressure



from a hematoma or heterotopic ossification; 2) prolonged coma; 3) severe spasticity; 4) improper positioning; 5) fractures; and 6) improperly applied casts (199–201).

It has been estimated that 50% of these neuropathies are preventable (199). Thus, in the acute care setting, preventive measures are incorporated to the rehabilitation intervention such as proper positioning, monitoring of cast application, and the early treatment of spasticity and heterotopic ossification.

### Heterotopic Ossification

The risk of developing heterotopic ossification in the traumatic brain injury survivor is 20% and the risk increases as the severity of injury, length of immobilization and duration of coma increases (202). Also, the presence of spasticity and fractures increase the risk, especially if the fracture involves an open reduction, internal fixation or if there is a joint dislocation. Heterotopic ossification usually involves the large joints of the body (hips, elbows, shoulder and knees). Excess bone formation can result in significant disability by severely limiting the range of motion of a joint. Progressive loss of joint mobility and markers of increased osteoblastic activity such as an elevated fractionated alkaline phosphatase level warrants a comprehensive musculoskeletal examination, three phased bone scan and x-rays to confirm the presence, distribution and extent of heterotopic ossification (203). However, plain radiographs may not demonstrate the presence of heterotopic ossification for one to two months after the initial onset. Osteocalcin, another marker of osteoblastic activity, does not appear to be useful in the early detection of heterotopic ossification or in assessing its maturity (203). Heterotopic ossification often presents as a soft tissue swelling and loss of range of motion. The differential diagnosis includes thrombophlebitis, cellulites, septic joint, fracture, hematoma or soft tissue trauma.

The treatment of heterotopic ossification initially involves preventive strategies; once heterotopic ossification formation has begun additional preventive and therapeutic interventions are initiated. Diphosphonates and indomethacin have been shown to prevent heterotopic bone formation (199,204). Diphosphonates may also minimize the extent of heterotopic ossification formation after its onset, but the role of diphosphonates in this setting remains controversial. The treatment of heterotopic ossification also includes physical modalities such as aggressive range of motion exercises in an attempt to reduce the likelihood of bony ankylosis (204,205). Other investigators discourage aggressive range of motion out of concern that the micro trauma or local hemorrhage may predispose the development of heterotopic ossification. In the relatively rare event that heterotopic ossification causes sufficient joint ankylosis to impede function, surgery is usually performed in combination with the radiation of

the involved area in the hope of regaining range of motion and arresting further bone development. However, surgery is often discouraged until one to two years after the onset of heterotopic ossification due to increased risk of recurrence during the active growth phase of the ectopic bone.

### INDIVIDUALIZED REHABILITATION PLAN

After documenting the extent of impairments and estimating functional outcome, the physiatrist is charged with determining the most appropriate rehabilitation interventions for the survivor. Early rehabilitation is initiated while the survivor remains on the trauma or neurosurgical service. Rehabilitation options following this early stage are predicated on the nature of residual impairments (170). In the unlikely event that a survivor of a severe traumatic brain injury recovers sufficiently during acute care to permit rehabilitation management on an outpatient basis, individual outpatient services or a day-treatment program may be recommended. Typically day treatment rehabilitation offers survivors integrated programs of physical therapy, occupational therapy, speech pathology, cognitive remediation, vocational and psychological services up to 8 hours per day, 5 days per week.

If, at the time of discharge from acute care, the residual impairments are of such severity that the patient remains dependent, then options include either an acute or subacute rehabilitation program. The typical admission to a traumatic brain injury acute rehabilitation unit is an individual who is able to consistently follow a 1 step command, is commonly confused and disoriented, restless if not overtly agitated, and many have a combination of physical limitations or medical complications. Ideally, it is the goal of this phase of rehabilitation to assist the patient from the late stages of unconsciousness through clearing post-traumatic amnesia, resolution of agitation, and at least minimal independence in activities of daily living. For the individual and their family, the most salient goal of the acute rehabilitation phase is to regain optimal independence in activities of daily living. To remain in this rehabilitation environment, the patient must be able to tolerate and benefit from a minimum of 3 hours of therapy, 5 days per week.

Subacute rehabilitation programs are largely nursing home based. These programs do not require that a patient tolerate 3 hours of therapy per day. Consequently, subacute rehabilitation programs are most appropriate for survivors who remain in the “coma stages”, responds to simple commands inconsistently or the rate of progress is slow. The typical length of stay is considerably longer than the present national average of approximately 21 days in acute rehabilitation. Largely because of staffing and overhead, subacute rehabilitation offers health care

providers a less expensive form of specialized intervention. Although data exist supporting the importance of early rehabilitation interventions on outcome (43,44), virtually no data exist comparing acute versus subacute intervention outcome.

After inpatient rehabilitation, a number of post-acute management strategies are available. Again, if the patient can be managed at home, then rehabilitation options would include individual in home or outpatient therapy, or comprehensive day-treatment services. If a patient in an acute rehabilitation setting fails to achieve basic functional independence in a timely fashion, then a transfer to a subacute rehabilitation program may be warranted. In the event that behavioral problems such as agitation preclude discharge to the home, more specialized inpatient behavioral treatment programs are indicated.

Another level in the continuum of rehabilitation includes transitional living programs. These are typically residential, community based treatment alternatives for individuals with primarily cognitive and neurobehavioral deficits that preclude independent living. The length of stay in a transitional living program may last as long as 12 months with the ultimate goal being independent living.

The final stage in the rehabilitation continuum includes vocational rehabilitation. This stage in the recovery process is initiated a number of months post-acute injury. Hence, vocational rehabilitation, transitional living and even specialized behavioral programs are rarely relevant or pressing program options to consider during the initial psychiatric evaluation.

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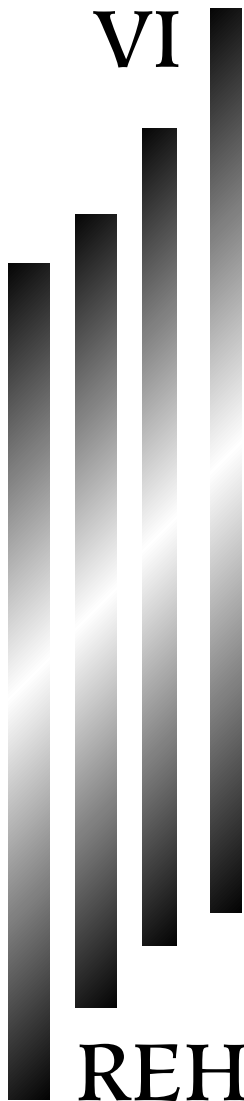
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**REHABILITATIVE CARE  
AND TREATMENT OF  
SPECIFIC POPULATIONS**



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# 20

## TBI: A Pediatric Perspective

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**S**erious illness in any child is a highly stressful event for all concerned: the child, parents, and family. Traumatic brain injury (TBI) can be particularly devastating. The injury commonly causes a variety of physical, emotional, cognitive and behavioral impairments. These impairments appear at a time of particular developmental vulnerability, and can significantly impact the child's ability to what children ordinarily do: grow, play, develop, learn, make friendships and gradually evolve into independent young adults. In an instant, parents' expectations for their child may be dramatically altered, and there is often no one in the health care system that can provide them with reliable information on recovery and prognosis.

Although many of the problems faced after brain injury in children occur in adults as well (e.g. seizures), children face a number of unique challenges in recovery. The following chapter will attempt to focus on those aspects of TBI which are unique to children.

### EPIDEMIOLOGY

Traumatic brain injury is the most common cause of acquired disability in childhood, with an incidence of approximately 200/100,000 per year in the United States. Incidence has been further broken down to 185/100,000

children for ages 0 to 14 and 295/100,000 adolescents and young adults (ages 15 to 24) (1). The leading cause of TBI varies with age. Pedestrian injuries and falls affect younger children while adolescents and young adults are more commonly injured in motor vehicle collisions and assaults. This rise in incidence at age 15 correlates with increased motor vehicle operation and assault (1, 2). The prevalence of TBI is twice as high in boys as it is in girls. Other factors associated with a higher risk of TBI are poverty, living in congested residential areas and parental instability (3).

### OUTCOMES

Of all children who sustain TBI, 95% survive (4); that number drops to 65% for those suffering severe TBI (5). Other studies have shown a biphasic association of age and survival after TBI. Highest mortality is in children less than 2 years of age with a gradual decline in mortality through age 12 and then a second peak in mortality at age 15 (6). With continued advancements in medical care, more and more children are surviving TBI. Survivor outcomes in pediatric TBI range from full recovery to severe physical and/or mental disabilities. It has been suggested that kids suffering TBI have better results in neurological and cognitive recovery compared with older groups. Using the Glasgow Outcome Scale (GOS), a study of 33 survivors

showed good recovery for 27%, moderate disability for 55% and severe disability for 18% (7). Generally children and adolescents do better than those older than 21, however it is important to note that children under seven do worse than older children (8, 9). A study looking at longer-term outcome (an average of 23 year follow up) reported 32.7% of survivors with physical complaints and 17.6% with psychological or psychiatric complaints (10).

Communication and cognitive dysfunction seems to contribute most to dependency. A study of 42 children and young adults found 37% of respondents were independent while 49% were dependent in some area of living. Of communication and cognitive deficits, memory problems contributed the most to dependence. Younger age groups and shorter duration of coma are associated with better functional outcomes. It theorized that improved functional outcomes for younger patients are secondary to greater plasticity in the younger brain. Also of note, chronic seizure or epilepsy can lead to greater dependence while presence of early seizures is not predictive of functional outcome (11).

## COGNITION AND PHARMACOLOGY

Cognitive deficits are a major contributor to disability following TBI, and this certainly holds true for the pediatric population. Cognitive impairments are manifest on many levels, including behavior, attention and memory (12). These changes probably are related to underlying alterations in cerebral neurochemistry. Brain injury results in a chain of neurochemical events beginning at the time of injury. Neurochemical changes have also been documented in chronic TBI.

Injury to a child's brain is particularly concerning because a child's brain is still developing. There are both immediate and long-term ramifications that result from pediatric brain injury. A child unable to learn new functional skills (physical and mental) as a result of a traumatic injury to the brain is severely disadvantaged as they progress to adulthood. Further complicating the issue is hidden deficits that may not be apparent immediately after injury. For example, one would not expect a three year old, healthy or impaired, to display higher level thinking; therefore a deficit might not be recognized until years later (13).

Arousal and attention are commonly impaired after injury, which often interferes with the patients' ability to process new information and consequently interferes with the rehabilitation process (14). Pharmacological interventions often target increasing arousal and attention. Tricyclic antidepressants, dopamine, norepinephrine and serotonin up regulators are often used (15, 16, 17). Conversely, pharmacological agents can sometimes interfere with arousal and attention, particularly antiseizure and

spasticity medications such as benzodiazepines and phenytoin.

Studies have shown a positive short-term effect of psychostimulants on behavior and cognitive functioning of adults with brain injury (18). While double blinded, placebo controlled, randomized studies of psychostimulants in the pediatric population are limited, there is some data involving methylphenidate. Methylphenidate presents perhaps the most intriguing possibility in the pediatric population because of its established use in attention deficit hyperactivity disorder. Williams et al. showed no significant difference between methylphenidate and placebo in terms of behavior, attention, memory and processing speed (19). However, the authors note some possible faults in study design including dosing, timing of intervention and length of intervention.

Many other drugs have also been used in the pediatric brain injured population, including tricyclic antidepressants, amantadine, atomoxetine and bromocriptine. Formal recommendations for pharmacotherapy in pediatric TBI are difficult to make because of the lack of solid evidence. White et al. point out that this is likely due to the lack of controlled studies, confounding effects of spontaneous recovery and imperfect outcome measures (20). While many drugs are used and often seem to have a clinical effect, further well designed clinical trials are needed.

## POST-TRAUMATIC SEIZURES

Post-traumatic seizures are typically divided into three types depending on their timing in comparison to the trauma. Seizures occurring within minutes of trauma are referred to as immediate seizures. Early seizures, by definition occur within one week of trauma, while late seizures occur beyond the first week on injury. A person who suffers two or more late seizures can be diagnosed with post-traumatic epilepsy. It has been established in adults that post-traumatic seizures and epilepsy adversely affect recovery from TBI. An overall decrease in quality of life is seen in these patients as a result from inability to work, social isolation and less return to leisure activities (21).

Studies have shown that children suffering TBI have a 3% to 9% incidence of early post-traumatic seizures, which is higher than expected for adults. This being said, the risk for late seizures is lower in children compared to adults (24–27). Severity of brain injury correlates directly with the incidence of epilepsy. Further illustrating this point is the fact that the greatest predictor of post-traumatic epilepsy is severity of injury (21). Appleton found that the only specific risk factor that was clearly correlated with the development of post-traumatic epilepsy (PTE) was early seizure occurrence within the first week after injury. The drugs they chose to use for treatment of PTE were carbamazepine or lamotrigine (22).

The morbidity and mortality associated with post-traumatic seizures and epilepsy has resulted in an effort to find medications to reduce the risk of both. Phenytoin has commonly been used as anti-seizure therapy in all groups with TBI. Early seizures have been shown to be decreased with phenytoin therapy, however phenytoin has shown no reduction of post-traumatic epilepsy (23). In addition, anticonvulsants may actually impede recovery. Therefore, if no seizures are documented in the first week, antiseizure medications should be discontinued. In cases when early seizures are present one is faced with a clinical dilemma, both the seizures themselves and the treatment may actually negatively affect recovery (21).

### **Deep Venous Thrombosis/Pulmonary Embolus (DVT/PE)**

Deep venous thrombosis and PE are seldom reported in pediatric literature and as a result there is limited information regarding thromboembolism and pediatric TBI. An incidence of < 5% has been reported in a general disabled pediatric population (28), further analysis showed one out of 185 children with closed head injury had a documented DVT (29). There are no current recommendations for screening for DVT in the pediatric population because of the low incidence. While DVT in children may present the classic with clinical signs and symptoms of leg swelling and pain, this is not always the case. A child may complain of only vague abdominal or inguinal pain. As a result, clinicians must maintain a high index of suspicion. General DVT/PE prophylactic anticoagulation is not currently recommended for prepubertal children (29).

### **PRECOCIOUS PUBERTY**

Precocious puberty is defined as the onset of secondary characteristics before age 9 in boys and age 8 in girls (30). Onset of precocious puberty in healthy children can take a severe emotional toll on both the child and family. Social difficulties also arise. The occurrence of precocious puberty in the child with a brain injury only magnifies these difficulties.

One study of 33 children with TBI found 7 to develop precocious puberty (31). Severity of brain injury does correlate with incidence of precocious puberty. Girls seem to be more at risk to develop this problem than boys. Of note, however is the fact that precocious puberty is seen more often in girls in the general population. While the exact cause behind precocious puberty following TBI is unknown it does not diminish the importance of the issue. Shortened adult stature can result as a result of early closing epiphysis. Clinicians should consider luteinizing releasing hormone (LH-RH) agonist therapy for a temporary and reversible treatment if precocious puberty is suspected (32).

### **HETEROTOPIC OSSIFICATION**

Heterotopic ossification (HO) is defined as ectopic bone formation that is seen in several medical conditions including central nervous system trauma, total hip replacement and burns. Incidence of HO in all TBI patients has been reported between 3% and 76% (33–35). In children and adolescents with TBI, incidence has previously been reported between 3%–20% (36, 37), depending on the methods used. An incidence of 22.5% was found using triple phase bone scan to screen all pediatric TBI patients, not just symptomatic children (38).

While there are no formal screening recommendations for HO, one must maintain a high index of suspicion. HO should be high on the differential when physical exam shows decreased range of motion, increased swelling or the patient complains of increased pain with joint movement. Further work up for HO should include triple phase bone scan and/or plain films.

The hips are the most common location for HO in children, followed by elbows, knees and shoulders (39). Several factors have been established as risk factors for HO. These include age older than 11 and coma lasting greater than 7 days. Multiple fractures have also been associated with increased incidence of HO. Perhaps the most concerning result of HO is that it has been shown to result in poorer functional outcomes (38).

Clinical findings often associated with HO include decreased range of motion (ROM), pain and swelling. DVT, infection and fracture can have similar presentations. In fact, there have been case reports of HO and DVT found simultaneously in pediatric patients (40). As in adults, the primary treatment of HO in children is ROM, both active-assisted and passive, as the mainstay. Etidronate has been shown to reduce the occurrence of HO in adults with severe head injury (41). A rachitic syndrome has been reported in a twelve year old boy with a brain injury and HO who was treated with etidronate. As a result, alternative treatment should be used in children (42). Nonsteroidal anti-inflammatory medications remain an option for treatment of HO in children. Indomethacin is often the NSAID of choice in treating HO. Pediatric dosing is recommended at 1–2 mg/kg/day divided in 2–4 doses, not to exceed 150–200 mg/day. Surgical removal of HO is rarely required and typically reserved for more severe cases, specifically when it interferes with positioning and personal care, which can lead to skin breakdown.

### **COGNITIVE/EDUCATION**

Neuropsychological testing is done to understand patterns of cognitive problems and to obtain information on the general level of a child's impairment. Testing can

estimate the child's pre-injury level of cognitive abilities by using some subtests that are less apt to decline with injury. Intellectual deficits are a relative factor depending on the child's pre-injury level of abilities. The pattern of cognitive assets and deficits that is found on this testing provides information for treatment approach in rehabilitation, as well as for school. It examines features such as whether someone is stronger at using verbal or visual learning and where memory strengths and weaknesses are, in order to formulate an effective treatment plan. Neuropsychological testing can also be performed to monitor a child's recovery pattern (43). The pattern of neuropsychological deficits depends on the developmental level at the time of injury as well as the hemisphere and site of lesion (44). Skills that are undeveloped at the time of injury may initially appear to be uninvolved, however as the brain becomes more mature, the impairment emerges (45). Children after TBI have been shown to have decrease in IQ, adaptive problem solving, memory and academic performance, along with psychomotor problem solving, compared to children without injury. The impairment on the testing is more severe in more severely injured children (46). IQ scores are minimally affected but testing shows decrease in speed and efficiency, more significantly with more involved children. Most of the children tested had few deficits from the TBI (46).

Bowen evaluated 22 children post-TBI and found no reliable association between neuroimaging data and cognitive measures, but found that children with more diffuse injury on scan did more poorly on the testing (47). Levin looked at 76 children with TBI and did find that the size of lesion on MRI was related to abnormalities in cognitive performance. He also found that cognitive impairment was more dramatically shown in children up to 10 years old than in teens (48).

Multiple studies have shown increased need for educational support and special education after TBI (49–53). One study of children with severe versus mild to moderate TBI showed significant effect in reading recognition, spelling and arithmetic scores in those with severe level, along with lower relative scores for teens than children in all levels of severity. This study also showed significant improvement from baseline to six months of injury but no change from six months to two years. They also found average achievement test scores at two years after TBI but 79% of the severely injured group were receiving special education or had failed a grade (54).

The effect of TBI on a child's language development has also been studied. In children there is more of an impact affecting linguistic abilities, where older children and teens have more of a disruption in higher order communication functions common due to the developmental level (55). More severely affected children have been shown to have more deficits in language skills (56).

One study examined pre-injury behavioral and learning characteristics of children, based on teacher assessment. There was a somewhat higher instance of pre-morbid behavioral problems in children with TBI. The TBI group also tended to include children of lower socioeconomic status (57). In those with behavioral difficulties after TBI, it is difficult to predict their prognosis. Behavioral evaluation can include many sources from throughout the environment. There is likely an interplay between cognitive deficits and behavioral difficulties (43).

Complex problem solving and abstract reasoning are high levels of cognitive processing. Difficulties with this affect new learning abilities and the ability to benefit from feedback and to solve problems. Being efficient in organizing activities in logical sequence can be impacted, as well as initiating and modifying behavior. This can lead to difficulties socially and in school (43).

Difficulty with executive function, in particular, reduced initiation and persistence, poor planning, poor organization and difficulty correcting errors are frequently seen post-TBI. This frequently leads to dissociation between a child's ability to verbally describe an activity versus an inability to actually perform the task. This may be related to deficits in speed of processing information. This may give the false appearance that a child is non-compliant with school requests (43).

## FAMILY

A child incurring a TBI can have a significant impact on the whole family. The entire spectrum of family life can be impacted from emotional to financial. Parents have reported difficulty with maintaining work schedules, as well as financial difficulties, secondary to injury and care for the child post-injury. Children who are hospitalized for longer or who had multiple types of injuries had families who were most impacted (58). Approximately one third of families in one study reported that there was a deterioration in their family financial status since the child's injury and just under 30% reported that an adult lost a job, either through firing or quitting due to their child's care needs (59). The family medical leave act (FMLA) should decrease the number of firings due to a child's severe injury but will not eliminate them. Changes in housing, also, are sometimes required and can also have a financial impact (59). Siblings can also suffer adverse consequences. One study demonstrated that over 50% of families had siblings with behavior problems, withdrawal from their injured sibling, and increased fearfulness (59). Conversely, fifty percent of families described that siblings became more involved in their family after injury. They also described decrease in school performance and difficulty with peer interactions (59). McMahon found no statistically significant difference in depression, self-concept

or behavior between siblings of children who had TBI and classmate controls. However, she did find that siblings of children with the most severe injuries did have a significantly lower self-perception, as well as, more symptoms of depression (60).

The importance of family needs and the percentage of needs that were unmet was a cause of significant amount of variability in family stress (61). Comparison of families with children with TBI versus other reasons for hospitalization has shown that parents of children with TBI are more likely to have unmet needs, including medical information, professional and community support, and a feeling of involvement in the child's care (62). One means of attempting to minimize the stress has been approaching the need for information by giving pamphlets about TBI (63). Snowdon described improving parental satisfaction by approaching the family's need for information, as well as, their need for social support (64). It has been described that the primary protection from a high level stress on the family and depression in family members of someone with TBI is a large amount of social support for the family (65). The number of medical problems was also found to be related to parental stress, with approximately one third of parents of children with TBI showing decreased psychological health (66). Social support was felt to be the biggest protector against psychological distress of families. If there was not adequate social support, caregiver distress was worsened with further time out from injury, cognitive dysfunction of the child, and unawareness of deficits by the child; but, if the social support was strong, these were not distressing factors (67).

The family also was found to have an impact on behavior and recovery of the children with TBI. Parental support and parental acute emotional reaction to the injury were predictive of the child's behavioral outcome in the first two years of TBI. This was believed to indicate the importance of the parents' coping on the child's development of behaviors (43). Psychosocial outcome in children post TBI has been described as more closely linked to pre-injury family function and behavior than to injury severity (68).

Coping strategies of the family have an impact on the stress of TBI in a child over the long-term period. Sixty percent of all families experience a change in their structure after TBI, showing changes in coping style, including cohesion and family roles (69).

It has been described that parents who are undergoing economic or personal stress more frequently respond punitively to their children. This may lead to the children then reacting with worse behavior in response (70). The stress of a TBI may adversely affect the parent-child interaction, which may then further exacerbate the child's behavior. Therefore, criticism by and conflict with the parents are seen more frequently with children with adjustment difficulty (71). High levels of parent-teen

conflict have been shown to be related to higher risk of delinquency (70). Increase caregiver stress contributes to more negative interactions with their children (70).

In a study comparing children with TBI versus orthopedic injury, the group with severe TBI has similar levels of criticism and coldness as well as personal engagement and levels of conflict as did the group with orthopedic injuries (72). They did find that higher levels of criticism, coldness and conflict were associated with worse outcomes for those with a TBI (72). This study showed association between parenting conflict and criticism, with adjustment long-term in parent and patient. This suggests that decreasing conflict and criticism in the relationship may improve long term functioning on both sides (72).

## SOCIAL/BEHAVIORAL

Success in social interactions is a key to positive outcomes in most areas of life. Social skills include the ability to understand another's feelings and the ability to interpret social cues and to predict and evaluate social/behavioral consequences (73). Social success is a combination of social skills, behaviors, and other factors such as athleticism and attractiveness (74). Social competence is felt to be a fundamental basis to developing friendships and to having positive evaluations from others (75). Impairment of social skills is correlated with poor social outcome (76).

It has been reported that the interrelationship of language, executive function and self-managing behavior may be the basis of social impairments associated with communication disorders (77). Chapman has demonstrated that traditional language tests underestimate communication difficulties in children with traumatic brain injury due to their difficulty with sequencing, developing resolutions, and obtaining the moral of a story, particularly if the frontal lobe is involved (78). These problems can have significant effects on the child's ability to interact in an acceptable manner with family, other children, and school personnel (79). Teenagers are at a key time for developing cognitive communication skills, to interpret implied meanings, particularly including sarcasm, negotiation, and complicated pragmatic cues. These skills may be compromised with a TBI during these years, thus compromising social abilities (80).

Cavell has described that social competence is measured at the following three levels: social skills, social performance on specific tasks, and social adjustment (74). Most testing examines social performance but not social skills. The latter includes the ability to perceive and interpret situations, decision skills that require the ability to determine expected outcomes of behavior, and, therefore, make decisions based on these, and enactment skills, which demonstrate the ability to generate a response (74).

Social skills frequently reported as impaired in adolescents with TBI include attentive listening behavior, perception of non-verbal cues, detection of sarcasm, sharing equal conversation burden, humility, and speaking at the listener's level (79). Turkstra studied normally developing teens and teens with TBI, looking at conversational skills. They examined the conversation skills of both, studying the emotions of anger, irritation, happiness, sadness and disgust, with consideration of the teens' self-regulation of behavior as well as intelligence. They found no impact of gender, intelligence, or race on emotions or conversation ability. They did find that teens with TBI performed more poorly on identifying emotions, though their errors were similar to the control group of teens. On evaluating the accuracy of conversations, the teens with TBI had many more errors and with a pattern that was unlike the errors made by the control group of teens. They had the most difficulty with the ability to detect sarcasm and the response to sarcasm, and also had difficulty with identifying bragging and a response to bragging. They found no correlation between vocabulary and the ability to identify emotions or intent in conversation. The teens with TBI had significantly more difficulty overall with detecting and evaluating social behaviors. The fact that sarcasm and bragging were the most difficult areas of evaluation was interpreted to mean that there was greater difficulty in social inference, particularly with different explicit and implicit messages (76).

Social success depends on effective self-regulation of cognitive and social behavior (81). The surrounding environment and supportive behavior of others can exacerbate or improve self-regulatory impairment in those with a TBI. Interventions to address these deficits, therefore, need to be sensitive to the child's social context, and the child or teen's daily activities are key to address in attempting to improve the performance of executive function related abilities (81).

Social functioning is a critical predictor of quality of life (82). Children with TBI are more concerned about losing friends than about success in schoolwork, their health, their ability with sports, or getting in trouble at school (83). An intervention program for children with TBI, called "Building Friendships", was described with a team of child/parent peers and school staffs to meet periodically, set an action plan, and increase the number of social contacts for the students (84). Unfortunately, the program was not found to sustain itself once facilitators had stopped their involvement.

Social function is shown to improve during inpatient rehabilitation stay with children and teens with TBI, with those with the greatest deficits showing the greatest gains (85). Social function skills are shown to continue to improve after return from rehabilitation to home (86).

In a multicenter study of 65 children and teens, only 3% to 27% were reported as ready for age-expected

participation at discharge in home, school, and community life, with social/behavioral deficits responsible for the majority of limitations (87). The Come Back Programme is a program for teens and young adults after TBI and after their initial rehabilitation program that had continued psychosocial deficits. The deficits reported were in independent living, employability, relationships, and contact with friends. In a follow up study one year or more after the completion of the program, there was no improvement seen in contact with family or leisure activities, however there was improvement in employability and independent living, but not back to the level of pre-injury (88). Their recommendations were for a second rehabilitation program, such as this, for psychosocial deficits as well as follow-up support and structural control for continued success (88). A program in New York worked with 80 individuals with TBI who had severe behavioral deficits at least two years post injury. This program's approach was long-term practice of participation-enhancing and disability-reducing strategies to result in automatization and internalization of strategies to reduce the impairment (89). Critical components were described as intervention being in context with the person's life and teaching those directly involved with each life how to perform this intervention. They found with these customized supports that they had a cost-effective improvement in quality of life for the individual and their loved ones, and greater than 80% of those with significant behavioral disorders were returned to their home communities (89).

Behavioral changes and difficulties have been widely reported in children after a TBI. Stancin found that 89% of parents of children with TBI interviewed reported behavioral change post injury (90). A British study described two thirds of the children with TBI with significant maladaptive behaviors several years post injury (91). A French study showed a higher frequency of depressive tendencies in teens with TBI, as well as, behavioral problems and a lack of self-awareness of the behavioral problems (92). In a phone interview of parents of children and teens one year after TBI, 40% of the children were described as having behavioral problems (93).

Psychiatric disorders are sometimes described after TBI in children and teens. One study evaluating the first three months after TBI showed that in the short term, children with more severe injury, previous psychiatric disorder, family psychiatric history, dysfunctional family, or lower socioeconomic class had high risk of a new psychiatric disorder (94). In looking at psychiatric disorders one year post TBI in children and teens, attention deficit hyperactivity disorder and depressive disorders were the most common diagnoses described, both new onset and previous. For new diagnoses, which were reported in 48% of the children studied, 74% persisted. Internalized disorders are more likely to resolve than externalized disorders (95). Interestingly enough, this study attempted

to exclude children with pre-injury psychiatric disorders but found 16 children with 20 previously undiagnosed disorders, primarily ADHD and anxiety disorders (95). Emotional distress may actually increase over time. Depression is commonly seen later as increases in cognition and self-awareness lead to recognition of deficits and, with that, depression (43).

Early agitation post-TBI may be a combination of an inability to filter out excessive stimulation, poor memory and cognitive limitations. This may manifest as combinations of old familiar memories intruding in current events and may appear to be psychiatric disturbances, but are in fact neuropsychologically based misperceptions (43).

In a broad ranging, greater than 25 year follow-up of 39 individuals in Finland who had TBI during the preschool years, it was reported that 59% of the children attended typical school, 21% attended a school for the physically disabled, and 18% attended a school for the mentally retarded. Only twenty three percent of adults worked full time in regular work environment with 26% working at a sheltered work place. With finding a large discrepancy between 59% reportedly having normal intelligence and normal school performance and only 23% in a regular full time work environment, it was interpreted to indicate that school performance or intelligence evaluation is not a guarantee for a good long-term prognosis (96).

## CONCLUSION

The bromide that "children are not small adults" certainly holds true for pediatric brain injury. The unique emotional, social and developmental needs of children demand a holistic and comprehensive approach by a broad-based team. Families also require special care to help calm the inevitable turmoil created by a life-changing injury. This care is ideally provided by a team of specialists with experience in brain injury, and in the care of children.

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# 21

## The Older Adult\*

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### DEMOGRAPHICS OF AGING

The older adult or geriatric population includes all individuals aged 65 years and older. This chronological cut-off is arbitrary and more related to federal statutes (in the United States, Medicare and Social Security Administration Retirement) than scientific standards. Improvements in standards of living and health care have led to greater life expectancies, as well as increased survivability from injury and disease, resulting in a significant increase in the number of older adults. Currently, 12.4 percent (35 million people) of the U.S. population are aged 65 years and older. This percentage of older adults will rise to 21 percent (64 million people) of the population by the year 2050. In addition, those 85 years and older (the so-called *oldest old*) will increase from 1.4 percent (3.9 million people) to 5 percent (15 million) in that same time frame (1). For this chapter *older adults* are those aged 65 years and older, unless otherwise noted.

### DISABILITY IN THE OLDER ADULT

More than 1.5 million (4.5%) older adults reside permanently in a nursing home and require functional

assistance (1). According to the most recent data, more than ninety percent of all community dwelling (including assisted living) older adults have no reported deficits in everyday functional abilities (2). Interestingly however, 40% report having a “disability” on their 2000 census (3). The limitations reported by the 6 percent who do report deficits are walking (19%), bathing (10%), getting outside (10%), getting in and out of bed (8%), dressing (6%), toileting (4%), and self-feeding (2%). Unfortunately, only 10% of these individuals reporting limitations actually receive assistance with these functional activities. The need for functional assistance increases with increasing age, and nearly 40% of individuals 80 years and older require help (2, 4).

### ETIOLOGY OF INJURY AND INJURY PREVENTION

Next to teenagers and young adults, older individuals have the next highest rate of hospitalization for TBI, with an annual rate of 121 per 100,000. It is the only age group where females and males have similar rates of injury. In the United States, Caucasians had 1 1/3 the incidence of

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Asians, 1 1/2 that of African-Americans and over 2 times that of Native Americans (5).

Unlike their younger cohorts, older adults sustain the majority of TBI's in domestic falls. Adults over 85 years old are 16.4 times more likely to sustain a TBI from a fall than those less than 65; 75–84 year olds are 7.6 times and 65–74 year olds are 3.1 times as likely. Moreover, the home discharge rates are 30% for those greater than 85, 41% for those 75–84, and 54% for those 65–74 compared to 86% for those less than 65 (6).

Risk factors for falls have been stratified into the following groups: 1) chronic, such as neurologic disease, sensory impairment, or musculoskeletal disease, particularly affecting the lower extremities; 2) short-term, such as episodic postural hypotension, acute illness, alcohol use, or medication effects; 3) activity-related, such as tripping while walking, climbing ladders, descending stairs or riding a bicycle; and 4) environmental, such as ill-fitting shoes or trousers, non-secure throw rugs, or poor lighting (8) These risk factors for falls also predispose the elderly to motor vehicle, pedestrian, and recreational accidents, any of which may result in TBI. The decrease in reaction time and walking pace commonly seen in the older adult additionally predisposes them to motor vehicle and pedestrian-motor vehicle accidents, respectively. Management of these risk factors includes scheduled, consistent, and competent primary physician care to minimize medical morbidities, regulate medications, and provide ongoing education. Additionally, focused rehabilitation interventions can be utilized to maximize physical abilities (gait, balance, strength), procure adaptive and assistive devices (canes, walkers, handicap parking stickers), and provide education. Finally, efforts to reduce violence against older adults are necessary to prevent this increasing cause of TBI.

### MECHANISM AND PATHOLOGY OF INJURY

Severe trauma in individuals over age 70 is six times more likely to cause intracerebral lesions than severe chest, abdominal, or pelvic injury, a trend that begins at age 40 years (9). Falls tend to result in focal brain injuries, most commonly subdural hematomas (SDH) and/or focal cortical contusions, usually involving the frontal and temporal lobes. These contusions may occur in multiple foci that appear on computed tomography (CT) scan several days after injury (10). Individuals on anticoagulation therapy for cardioembolic risk prevention or with coagulopathy from other medical conditions will have a greater likelihood of intracranial hemorrhage after a fall. Immediate loss of consciousness implies some degree of diffuse axonal injury (DAI) that can also occur with falls and portends a worse prognosis.

Motor vehicle crashes that injure older adults are commonly low-speed collisions, unlike the high-speed

collisions more typical of young adults. However, even these collisions can result in DAI in these individuals (11). Focal contusions and SDH's are also common in motor vehicle crashes.

Pedestrian-motor vehicle collisions in older adults frequently occur at crosswalks and in parking lots. They can result in DAI, focal contusions, and/or extra-axial lesions, most commonly SDH's. Individuals with these injuries are the most likely to have skeletal trauma, especially visceral injuries and pelvic and lower extremity fractures.

While assaults are a much more common cause of TBI in the middle-aged group, there is evidence that violent acts against elders are increasing, particularly in urban areas. These injuries invariably result in focal cortical contusions, skull fractures with SDH's and epidural hematomas (EDH), and intracranial bone and bullet fragments.

The injury severity profile of older individuals who survive their acute injuries and transition directly to acute rehabilitation differs from younger cohorts. In the NIDRR TBI National Data System (1989–2002, n = 3279:  $\geq 65$  years old = 259 subjects,  $< 65$  years old = 3020 subjects; all subjects are admitted to a model system emergency department within 24 hours of injury, are at least 16 years old, have acute trauma care followed immediately by acute inpatient rehabilitation), 71% have initial GCS 13–15 age  $\geq 65$  (27%  $< 65$  years), 14% have GCS 9–12 (19%  $< 65$  years), 7% have GCS 6–8 (28%  $< 65$  years), and 8 % have GCS 3–5 (26%  $< 65$  years). Time from injury to ability to follow commands is one day or less in 68% of those  $\geq 65$  years (39%  $< 65$  years), 2–7 days in 17% (29%  $< 65$  years), 8–31 days 25% (12%  $< 65$  years) and greater than one month in only 2% (7%  $< 65$  years). Computed tomography scans demonstrate no differences in degree of lateral shift or brainstem compression with regard to age group. Subdural hematomas occurred in 55% those  $\geq 65$  years (38% those  $< 65$  years) and EDHs in only 7% (11%  $< 65$  years). Bone and or metal fragments from open head injuries occurred in 3.1% those  $\geq 65$  compared with 6.9% of those less than 65 years old. Subcortical contusions in basal ganglia, internal capsule, pons, brainstem or cerebellum occurred in 9.1% those  $\geq 65$  compared with 17.3% of those less than 65 years old. The number and frequency of cortical contusions, subarachnoid (SAH) and intraventricular hemorrhages was not more than 3% different between the older and younger age groups (12). These findings are reflective of the increased likelihood for older individuals to suffer falls and resultant focal cortical injury with less time in coma compared with the higher incidence of subcortical injury in younger individuals. They are also more likely to incur SDH due to relative brain atrophy and fragility of bridging veins than younger individuals.

## MORTALITY

From 1989 to 1998, TBI-related deaths decreased in all age groups except those greater than 75 years, where the rate increased from 50 to 60.5 per 100,000. For that age group, falls, firearms and motor vehicles were the external causes, in that order of frequency, whereas for the 65–74 decade, firearms were the most frequent cause. Starting at age 55, mortality from firearm-related TBI was more common in Caucasians than African-Americans with the rate increasing every decade (13). An earlier CDC survey from 1980 to 1992, indicated that suicide was the third leading cause of traumatic death in those over age 65 after unintentional falls and motor vehicle crashes. Divorced and widowed men were in the highest risk group (14).

The largest group of older individuals with TBI studied in a neurosurgical population is from Rambam Medical Center in Haifa, Israel, consisting of 263 individuals. Mortality rate was 18%; however, many patients were transferred from other centers and had thus survived their initial injuries. The highest mortality group were those with subdural haematomas (33%), followed by contusions (27%), diffuse axonal injury (11%) and chronic subdural haematomas (3%) (15).

Smaller sample size studies from the early 1990s have indicated 80 % mortality and greater, with the great majority during the first 2 weeks of hospitalization. Subdural hematomas (SDH) requiring evacuation were the most common contributing cause of death. Cardiac, pulmonary and multi-system failure were more common in the older than younger individuals, but never exceeded 33% as the main etiology of death (16, 17). One research group proposed that it was futile to treat those over 80 years old with a GCS < 10, given the high degree of mortality and severe disability (18).

In clinical practice it may be difficult to limit the number and degree of interventions performed unless there are clear advanced directives giving relatives and health care providers guidance.

## MORBIDITY

### Multiple Trauma and Hypotension

Severe multiple trauma as measured by the Abbreviated Injury Severity (AIS) score is less common in older than in younger age groups. Hypotension and multiple trauma are closely associated. Severe multiple trauma without hypotension or hypoxia has not been associated with worse outcome as measured by the Glasgow Outcome Scale (GOS) (16).

Cerebrovascular events can occur as a result of hypotension in the peritraumatic period; strokes caused by thromboembolism, thrombosis, or ischemia from

massive swelling are uncommon causes of peritraumatic stroke in older adults.

## Fractures

In the NIDRR National Data System skull fractures occurred in 23% of those  $\geq 65$  years old compared to 37% under 65 years; lower extremity or pelvic fractures in 15% and 25%, upper extremity fractures in 12% and 13%, spine column fractures in 15% and 17% respectively. Combinations of TBI and spinal cord injury are 2–3 times more common among younger individuals (12).

## Medical Complications

Respiratory failure requiring mechanical ventilation for more than 7 days occurs in 22% of those  $\geq 65$  years old compared to 40 % of those less than 65 years of age who go to acute rehabilitation. Gastrostomies or jejunostomies were prevalent in 23% and 35% respectively (12).

Acute anemia occurs in nearly all individuals who incur trauma. Older individuals have poor tolerance for blood loss. Anemia may effect energy level, tolerance for activity, appearance and overall sense of well being. Laboratory values may not reflect lowered hemoglobin levels until after rehydration occurs as a result of iatrogenic effects of diuretics, mannitol, and bedrest which can result in lowered intravascular volume and relative hemoconcentration. Coagulopathy requiring the use of fresh frozen plasma or platelets occurred in 7.4% of those over 65 and 7.3% less than 65 years old (12).

## FACTORS AFFECTING OUTCOME

### Age and acute injury recovery

Most of our knowledge about outcome of older adults with TBI comes from studies involving all age groups. These investigations report the positive associations between increasing age and mortality (19–24). Several studies have examined the functional outcomes of older adults who survive brain injury (11, 19, 25, 26, 28). The majority of these investigations demonstrate poorer prognosis for the older than the younger adult, with a correlation noted as young as 40 years of age.

Looking at acute hospital discharge data, the CDC reported increasing length of stay for each advancing age decade. Only 55% of older individuals were discharged home compared to over 78% for all other age groups. Thirty-five percent were discharged to another facility compared to less than 13% for all other age groups. Acute hospital discharge outcome as measured by Glasgow Outcome Scores indicated that only 57% of older individuals had “good recovery”, 16% had moderate disability

and 11% had severe disability; in all categories, older individuals had worse outcome (5).

An injury severity matched analysis of data from the NIDRR TBI Model Systems from 1989 to 1995 revealed that individuals aged 55 years and older had twice the rehabilitation lengths of stay and costs, half the rate of functional recovery, greater cognitive impairment at discharge, and twice the nursing home placement rate of individuals who were aged 50 years and younger. At discharge the level of physical impairment was comparable for the two groups (29). From 1995 to 2002, rehabilitation LOS averaged only 5 days longer in those individuals older than 55 years compared to those 15–55 years old, Disability Rating Scale (DRS) and Functional Independence Measure (FIM) indicated more disability, and discharge to a private residence was 80.8% compared to 94.3% (30).

Further analysis of this data set through 2002 without injury severity matching demonstrated that those  $\geq 65$  years old had mean acute care and rehabilitation length of stays of 20 and 30 days, respectively. This corresponded to mean acute care costs of \$93,758 and inpatient rehabilitation costs of \$43,306. Length of stay and costs did not differ appreciably in older versus younger age groups. The discharge rate to a private residence was 67% for those  $\geq 65$  years compared to 87% in those  $< 65$ . At one-year post TBI, 80% of those  $\geq 65$  years lived in private residences versus 92% of those  $< 65$ . Disability Rating Scale (DRS) scores were one point worse for the older adult group at rehabilitation discharge and at 1-year post TBI (12).

At acute rehabilitation discharge, the median DRS level of functioning subscale score was 3.0 for those  $\geq 65$ , indicating requiring another person in the home, compared to 2.5 for those less than 65, indicating between needing a non-resident helper and a resident helper. Fourteen percent required placement in a skilled nursing facility (12).

Using two separate measures of independent functioning, the Disability Rating Scale (DRS) and Supervision Rating Scales (SRS), individuals  $\geq 65$  required and received higher degrees of supervision for their day to day care at one-year post TBI. On the DRS level of functioning scale, the median score for those  $\geq 65$  was 1.5, indicating between “independent in a special environment and requiring a non-resident helper,” while the median score for those less than 65 is 0.5, between “completely independent and independent in a special environment.” On the SRS, the median score for those  $\geq 65$  was 4, indicating overnight and part-time daily supervision, compared to 2.0 for those less than 65, indicating unsupervised overnight but living with another person who is not always present (12).

This association between age and outcome is of course quite complex and appears to be associated with the severity of injury as measured by initial GCS, duration of coma,

and duration of post-traumatic amnesia (PTA). The relationship between injury severity, particularly the GCS motor component, duration of coma or PTA and outcome that has been established in younger individuals probably applies to older individuals as well (6, 11, 17, 23, 31, 34, 35). Analyses from the Traumatic Coma Data Bank noted an association between those  $> 40$  years old and both mortality and poorer functional outcome as measured by the GOS. The relationship was further strengthened when initial GCS motor score and evidence of midline shift or cisternal compression was noted on initial CT scans (36). No other published TBI datasets have focused on the potential impact of mechanism of injury, neuropathology, associated injuries, or premorbid conditions on outcome in older adults. Other factors that appear to have some impact on the association between age and outcome include: a history of acute or chronic alcohol intake, post-injury depression and/or agitation, and a variety of formal and informal social support factors (6, 11, 17, 23, 31, 32, 37, 39). In contrast, other studies have demonstrated that favorable outcomes are achievable in the older adult with similar costs (33).

### Age and health after TBI

Individuals  $\geq 55$  years old living in the community who have experienced TBI within 4 years have more perceived health problems than age-matched controls. In a group of 49 individuals with TBI, prevalence of headache, thyroid problems, body temperature changes, skin and hair changes, headaches, speaking and understanding others, sensory changes, difficulty with movement and spasticity, sleeping problems, neck and back pain, were all greater than 30 age-matched controls (41).

## REHABILITATION

### Assessment

*Medical* The rehabilitation approach to an older adult after TBI is similar to the general geriatric rehabilitation approach with some specific modifications. Clearly, an understanding of pre-injury activity levels, cognitive limitations, behavioral issues, and chronic medical conditions is vital. This information will assist in the assessment of the potential physiologic reserve present prior to acute injury, which can assist in the immediate determination of an individual's readiness and appropriateness for specific rehabilitation interventions (i.e., specificity, intensity, and goal setting for therapies). Direct communication with the individual's primary care physician (PCP) or geriatrician can help to better understand the level of pre-morbid abilities and limitations and facilitate their specific management strategies into the rehabilitation program. This step is of additional importance for patients in managed care

networks, in which the PCP is often the gatekeeper for both current and future medical resource management.

An assessment of the acute medical and neurological status of the older adult with TBI must include a thorough evaluation of their medical systems, taking into account pre-morbid deficits. Screening of special senses (hearing, vision, touch) can provide useful information to the therapy treatment team on ways to optimally interact with the patient. While cerebrovascular, cardiovascular, metabolic and pulmonary diseases are common in this population, an appreciation of the clinical manifestations of these conditions will allow one to best structure the rehabilitation interventions. Joint and muscular abnormalities, especially pain, should be determined to help guide necessary management strategies and precautions. A thorough review of the patient's pre-injury and current medication routine is seminal in order to optimize treatments (e.g., pre-morbid medications may not have been restarted, numerous medications that are especially cognitive-impairing may no longer be necessary), define therapy parameters (e.g., anticoagulant use, antihypertensives), and prevent secondary conditions (e.g., antithrombotics are often underutilized in the frail older adult patient).

While serial brain-imaging studies are commonplace for patients with recent TBI, special attention should be paid to the presence of late or delayed bleeding and hydrocephalus. A follow-up imaging study, usually a CT scan, performed between 2 and 4 weeks post-injury can rule out these abnormalities, particularly if there has not been clinical improvement as expected. Indications for a MRI or dynamic imaging studies in the acute period after TBI would include unexplained clinical findings, such as brainstem pathology or a concomitant ischemic event. The patient's cognitive and behavioral status, diurnal variations in alertness, and ability to tolerate both physical and mental activities should be determined by examination and evaluation in the acute care and rehabilitation settings. Formal neuropsychological evaluations have little role in this acute period, but may prove to be invaluable in the post-acute phase or rehabilitation.

*Social* Of equal importance is a comprehensive review of the social support network, which involves an understanding of both the formal and informal support systems available (37). Formal support systems include federal (Medicare, Social Security), state (Medicaid, Department of Rehabilitation Services, welfare, area agencies on aging), and local (adult day health programs, transportation, Meals on Wheels) resources. Informal supports include family, friends, and religious affiliations. Early involvement of family and friends in planning and implementing the rehabilitation program is vital. Older adults tend to have significant others who are either older, disabled, or deceased, thus they are more likely to have increased involvement of extended families in their systems of

support. Daughters and female caregivers are more likely to play a major support role, particularly a physical or hands-on one, than sons are. It is essential to clearly understand the older adult's pre-morbid and/or present role in the social structure to which they expect to return. Additionally, one must consider advanced directives, congruence of patient and caregiver's goals, and religious and cultural factors.

*Funding* A working knowledge of the most common funding mechanisms available for post-TBI care of the older adults is extremely important. In the United States, for example, 98% of the older adults are primarily funded by a single source, Medicare. Similarly, in Canada, Australia, New Zealand, and most European countries, the government funds the overwhelming majority of rehabilitation care for the elderly. With Medicare, while physician (inpatient, outpatient, nursing home) fees and home-health and outpatient therapy are currently paid at 80% of "reasonable charges," inpatient and nursing home rehabilitation services have recently received a significant modification in reimbursement transitioning from the TEFRA to PPS (Prospective Payment System) model. The PPS reimbursement rate is adjusted if the patient is discharged to a skilled nursing facility. Secondary or co-payment insurance varies as greatly in coverage as standard commercial insurers, but rarely pays for extended rehabilitation services. Long term care or catastrophic insurance is increasingly available and provides reimbursement for subacute rehabilitation and custodial care within skilled nursing facilities (SNF).

Medicare is a federally sponsored program, so its coverage is uniform throughout the United States. Within *managed care Medicare health plans*, benefits vary depending on the plan chosen. Any individual who has paid into the federal tax system for 40 quarters (or was ever married to someone who has) and meets any of the following three criteria is eligible for Medicare part A at no cost: 1) age 65 years or older, 2) disabled and on Social Security Disability Insurance (SSDI) for more than 2 years, or 3) has end stage renal disease. Medicare part A reimburses for durable medical equipment, inpatient, and SNF rehabilitation services. Medicare part B, which is available to individuals on Medicare part A for a monthly fee, reimburses for physician services, home health and outpatient therapies.

Medicaid (e.g., Medi-Cal in California) is a state-sponsored and, therefore state-specific program to fund health insurance for the medically indigent, pregnant women, and children. Medicaid inpatient, outpatient, home health, nursing home, durable medical equipment, and physician benefits vary from state to state. Recently, numerous *managed care Medicaid* programs have become available that have further increased the diversity of covered services, in this case even within a state. At present, Medicaid pays for more than 85% of all custodial nursing



home care in the United States. Older adults who continue to work or who have been disabled veterans, federal or railroad employees typically have different commercial or managed care insurance as their primary funding source.

### Settings

Older adults with acute TBI should have access to rehabilitative services in the appropriate environment for their capabilities. Although most patients can benefit from some type and intensity of services, individuals who are most appropriate for 15 or more hours per week of interdisciplinary inpatient or day rehabilitation therapy programming are those who demonstrate the following characteristics: 1) an acute or new disability that is significantly below pre-morbid baseline; 2) a support system that will allow for return to a community residential setting; 3) the ability to tolerate, participate in, and improve with therapies, and 4) have appropriate funding to pay for services and after-care needs. See Table 21-1.

A return to the most familiar, pre-injury living environment is the first choice for discharge, but when not feasible an alternative reschedule (another family member's home, adult group home or assisted living) is a second option. Individuals who do not need or cannot tolerate inpatient or day rehabilitation services and can be managed in the community will often benefit from home health or outpatient therapy services. Skilled nursing facility-based subacute rehabilitation services are appropriate for older adults who are unable to tolerate the intensity of acute rehabilitation or cannot be otherwise managed at home. Common rehabilitation options are outlined in Table 21-1 (38–40, 42). In summary, the chosen rehabilitation pathway(s) will depend on medical and nursing acuity needs, endurance for therapeutic activities, formal and informal support systems, patient and family goals, and funding options.

## MANAGEMENT OF THE OLDER INDIVIDUAL WITH TBI

### Medical Issues

An assessment of rehabilitation issues should be initiated in the ICU. Early controlled mobilization in and out of bed minimizes the effects of prolonged bedrest, especially pressure sores, muscle contractures, spasticity, venous thromboembolism, cardiac deconditioning, atelectasis, aspiration pneumonia, constipation, urinary retention and infection, and sensory deprivation (43). Rest periods and up-down schedules may be required to gradually increase tolerance to activity. Improved participation and motivation can be facilitated by involving the individuals

with TBI and family in goal-setting and focusing on functional tasks that are similar to home routines.

Day-to-day medical management of the elderly individual recovering from acute trauma must be diligent and thorough. When a consistent team of rehabilitation professionals is working with an individual every day, changes in medical status and performance are more likely to be discovered earlier than by a smaller team of a physician, nurse, and family member. Newly identified problems must be evaluated efficiently and appropriate treatment instituted so that these problems interfere minimally with progress toward rehabilitation goals. If the identified problem is unlikely to resolve quickly, then the entire team must be informed so that the goals can be reformulated or the patient transferred to a different level of care.

### Medication Management

More than 90% of the entire population over age 65 takes at least one prescription medication daily; most take two or more. In addition, over-the-counter remedies are used ubiquitously (44). During the acute traumatic period, previously prescribed medications may be inappropriate, not feasible to administer, or unknown to the acute management team. Invariably, medications are used to treat or prevent conditions associated with acute trauma. Common medications include proton pump inhibitors or histamine-2 blocking agents to prevent stress ulceration, anticonvulsants to prevent seizures, sedatives and/or hypnotics for agitation, antiarrhythmics for transient or chronic cardiac conduction events, narcotics and analgesics for pain control, aerosolized inhalers for respiratory problems, and antibiotics for diagnosed or presumed infection. Insulin is more likely to be used than oral hypoglycemic agents for blood sugar abnormalities in acute care settings.

Medication review with the acute treatment team is crucial as the individual is transitioned from emergent and acute care to rehabilitation settings. Families should be encouraged to bring in all medications that they find in the patient's home as well; they are likely to have been prescribed by multiple physicians. Nonessential medications should be tapered or discontinued as soon as feasible. Medications that must be continued should be prescribed in the simplest form—that is, the lowest frequency with the fewest pills, during typical waking hours and corresponding to routine activities for that person. Principles of drug absorption, distribution, metabolism, tissue sensitivity, excretion, interaction, and compliance should guide the physician's choice of medications for any given condition (43).

### Pain

Acute pain from trauma is either nociceptive from visceral, bone and soft tissue damage or neuropathic from

**TABLE 21-1**  
*Levels of Care and Types of Rehabilitation Service Options for the Older Adult with Brain Injury*

LEVEL OF CARE	THERAPY INTENSITY/FREQUENCY	THERAPY SERVICES	REIMBURSEMENT	TYPE OF SETTING	DURATION OF PROGRAM	COMMENTS
Acute care services	5–6 days/wk; 0.5–2 hrs/day	Multidisciplinary (MD, N, PT, OT, SLP, RT, SW)	Medicare, Medicaid private insurance	Acute care hospital	3–21 days	After injury to prevent bedrest complications, allow comprehensive rehabilitation assessment
Acute inpatient Rehabilitation	6–7 days/week; 3–5 hrs/day	Interdisciplinary (MD, N, PT, OT, SW, TR, PSY, SLP, RT)	Medicare, Medicaid some private	Acute rehabilitation facility free-standing or attached to acute Hospital	7–35 days	After acute care or subacute care; specialization in rehabilitation medicine and therapy
Subacute care	3–5 days/ week; 0–2 Hrs/ day	Multidisciplinary (MD, N, RT, PT, OT, SW, SLP)	Medicare, some private	Free-standing or attached to acute hospital	7–100 days	Specialize in respiratory care
Skilled Nursing Facility (SNF)	0–5 days/ week; 0–2 hrs/ day	Multidisciplinary	Medicare, Medicaid, some private	Free-standing	7–lifetime	If discharge to community setting not possible
Home health services	3 days/wk; 0.5–2 hr/day	Multidisciplinary (N, PT, OT, SLP, HHA, SW with MD order)	Medicare, Medicaid private	Patient's home	2–12 wk	Homebound for physical or cognitive reasons after acute/ subacute care, inpatient rehabilitation
Outpatient services	2–3 days/wk; 0.5–3 hr/day	Multidisciplinary (PT, OT, SLP, PSY, SW)	Medicare, Medicaid, private	Clinic	2–8 wk	Living in community with focused needs (language, mobility, ADL)
Day rehabilitation services	3–5 days/wk; 3–5 hr/day	Interdisciplinary (PT, OT, SLP, SW, PSY, TR)	Private insurance	After acute care hospital, inpatient rehab or day rehabilitation	4–8 wk	Sufficient endurance to travel and good informal support systems; may allow shorter acute hospital or inpatient rehab length of stay
Day care services	5 days/wk; 4–10 hr/day	Health care attendants; Outpatient therapies available for brief periods as needed	Medicaid (Partial)	Custodial care of community dwelling older adults who need supervision for safety or who need minor assistance	Indefinite	Cognitively-impaired individuals who are physically mobile and able to perform self-care ADLs with supervision-assist

Abbreviations: MD = physician; N = nursing; PT = physical therapy; OT = occupational therapy; SLP = speech and language pathology; SW = social work; TR = therapeutic recreation, HHA = home health aid; PSY = psychology; RT = respiratory therapy.

peripheral or central nervous system injury. In addition, older individuals are likely to have one or more chronic conditions, such as arthritis, osteoporosis, or peripheral vascular disease, that may contribute to their experience of pain. Comprehensive pain assessment tools are available and often need modification when individuals have cognitive impairments. The goal of pain management is improved function, mood, and sleep (45).

For nociceptive pain, analgesic medications and physical modalities are often necessary to facilitate mobility. Comfortable positioning, physical activity, heat, ice, ultrasound, and massage are preferred first line non-medication interventions (46). If pain is occurring at predictable times of the day or with routine activities, then non-narcotic analgesic medications can be scheduled for these activities. Individuals may be incapable of asking for medications or knowing their schedules. Often just the anticipation of pain deters individuals from activities. The practice of scheduling pain medications allows for better overall pain control and facilitates the individual's performance of activities in the acute rehabilitation process. Acetaminophen requires no dosage adjustment in the elderly and has equal analgesic efficacy to non-steroidal anti-inflammatory medications (NSAIDs) (43, 47).

If there is concomitant inflammatory arthritis or heterotopic ossification, NSAIDs and disease modifying medications may be indicated, with appropriate monitoring for gastrointestinal, renal and cardiovascular toxicity (48, 49). Nociceptive pain that disturbs sleep may be addressed with bed positioning and non-narcotic analgesia at bedtime. Narcotic analgesics are more potent in older individuals and invariably cause constipation and lethargy; they should be reserved for pain refractory to the above approach.

Neuropathic pain caused by chronic pre-existing conditions, such as diabetes mellitus or alcoholism, will likely require long-term maintenance treatment. Pain from peripheral nerve, plexus injuries, or subcortical lesions may cause acute neuropathic pain. Tricyclic antidepressants and anticonvulsants are usually more effective than analgesic medications for both acute and chronic neuropathic pain syndromes. Cognitive and autonomic side effects, toxicity and drug interaction profiles will determine which of these medications will be most safe in the older individual.

### **Deep Venous Thrombosis and Pulmonary Embolism Risk**

No standard of care yet exists for prophylaxis of deep venous thrombosis (DVT) after traumatic brain injury for any age group. In the acute hospital setting, DVT incidence was reported as high as 54% in those with "major TBI" (50). On admission to acute rehabilitation units the reported incidence ranges from 1.6–20% in

various studies (50–53). Sequential compression devices (SCD's) with or without thigh-length antiembolism stockings are considered safe if they are initially applied within the first 2–3 days post-injury. Data support their use for DVT and pulmonary embolism (PE) prevention if they can be applied 23 hours per day (54, 55). This amount of SCD use is most feasible in acute care settings until the patient is mobilized out of bed for more than a few hours.

Low-dose unfractionated or low molecular weight subcutaneous heparin are often contraindicated with recent intracranial surgery or subdural hematoma. No consensus exists as to the exact time that post-injury prophylaxis is relatively less risky than recurrent intracranial hemorrhage or expansion of cerebral contusions. It is probably safe for individuals with DAI within a week post-injury (56–58). Although low molecular weight heparin may be superior to unfractionated heparin in high risk trauma cases, bleeding risk after severe TBI may preclude use of either agent. If DVT is suspected, duplex ultrasound is the least invasive but adequately sensitive test to detect symptomatic disease without confirmatory venography which carries more morbidity (58).

### **Seizure Risk**

During acute care and inpatient rehabilitation the seizure frequency is 11% in those  $\geq 65$  years old and 12% in those  $< 65$  (12). Englander and colleagues followed individuals admitted to 4 trauma centers with TBI and intracerebral lesions for up to 2 years post injury. Individuals over 65 years old had 22.7% incidence of seizures compared with 18.7% between 16 and 64 years old, which was not statistically significant (59). Most posttraumatic seizures (PTS) are focal or focal with generalization, rarely progressing to status epilepticus. If PTS occur within the first week post TBI or if an individual receives prophylactic medication during acute care, anticonvulsants can be stopped abruptly (phenytoin, fosphenytoin, carbamazepine, valproic acid, oxcarbazepine) or weaned (diazepam, lorazepam, barbiturates) to minimize risk of withdrawal symptoms without increasing the risk of subsequent seizures (60). For those with higher risk, such as those with penetrating injuries, intracerebral hematomas requiring surgery, or multiple contusions, the use of padded side rails or enclosure beds can protect the person from further injury, should seizures occur. The continued usage of anticonvulsant medication after 7 days post injury even in such higher-risk individuals is not recommended by the American Academy of Neurological Surgeons or the American Academy of Physical Medicine and Rehabilitation (60, 61).

If seizures occur in the absence of a correctable metabolic disturbance after the first week post TBI, then there is an 86% likelihood of recurrence (62). The choice

of antiepileptic medication in older individuals is predicated on the same principles of choosing any medication for long-term usage: side effects, the degree of protein binding, drug interactions, cost, and compliance. Some of the newer antiepileptic drugs have fewer interactions, greater therapeutic windows, and do not require serum monitoring, such as oxcarbazepine and levetiracetam (63, 64).

### **Nutrition and Swallowing**

Older individuals with TBI are just as likely as younger individuals to have neurogenic dysphagia and more likely to have some pre-injury gastrointestinal condition that affects eating or digestion, e.g., dental problems, gastroesophageal reflux. Dentures may no longer fit properly after they have been removed for even several days during acute care.

Reestablishment of adequate nutrition is important in facilitating health and optimal recovery. Determining an older individual's ideal body weight and eating habits is a start, although many older people have compromised nutritional baselines. Up to 20% of ambulatory older individuals have a measurable vitamin deficiency (43). Serum albumin levels less than 3 g/dl or cholesterol less than 160 mg/dl are indicators of inadequate nutrition. Low serum ferritin or iron levels are also common post-trauma; enteral formulas have variable amounts of iron, so supplemental iron is often necessary to replace iron stores even with normal hemoglobin levels. Full replacement of iron stores may take 3–6 months (65). Following weekly or biweekly weights can help monitor nutritional status; if this is not accurate or feasible, serial midarm circumference measurements are more accurate than skin fold thickness in older adults (66). Commonly used medications are associated with the side effect of decreased appetite, especially selective serotonin reuptake inhibitors (SSRI), NSAIDs, digoxin, L-dopa, and diuretics. Other medications and conditions can decrease psychomotor skills for self-feeding, such as antipsychotics, sedatives and the injury itself.

In order to avoid aspiration pneumonia, bedside evaluation of swallowing capabilities should be performed as soon as the patient is sufficiently alert. Further evaluation with videofluoroscopic studies is best decided jointly by the physician along with the therapist who evaluates swallowing and those helping with feeding. These studies are most helpful when silent aspiration is suspected or when there is uncertainty regarding the best compensatory swallowing technique (67). Frequent monitoring for symptomatic aspiration by lung auscultation, listening for laryngeal pooling of food or liquids with breathing or spontaneous speech and coughing with proximity of eating and drinking are effective bedside monitoring techniques.

Until oral feeding can occur, appropriate enteral formulas are necessary. The smallest-gauge feeding tube should be used for optimal patient comfort. A gastrostomy may be preferable if prolonged enteral feeding is projected. Using formulas with fiber and starting with half-strength solutions are less likely to cause diarrhea. Lactobacillus supplements are often helpful in counteracting the tendency for loose bowel movements associated with recent or concurrent antibiotic therapy. Bolus feeding routines that correspond with eventual oral meal times makes transition to an eating routine easier and facilitates gastrocolic reflexes that aid in regular basel elimination.

### **Substance Abuse**

After dementia and anxiety disorders, alcoholism is the third most common mental disorder among elderly men in the United States (68). In older adults alcoholism is closely associated with tobacco abuse, other drug dependence, hypertension, liver disease, and organic mental disorders such as delirium, dementia, and amnesic disorders (69). A substantial proportion of older individuals begin to have problem drinking after the age of 60; others have a life-long habit (70). Ascertaining the history of alcoholism and other substance abuse in TBI is a challenge in and of itself (71). The CAGE questionnaire is the one of the easiest and quickest clinical screening tools (72). Using the Center for Disease Control and Prevention (CDC) screening tool at one-year post injury, 19.7% of individuals  $\geq 65$  years old admitted to any alcohol use compared to 39.1% of younger individuals. Of those that drank, no one  $\geq 65$  admitted to drinking more than 5 drinks per day compared to 12.8% of younger individuals (12, 73).

Treatment of substance abuse in the older individual poses unique challenges. Most programs are designed for younger adults, and the group experience may be less relevant for the older individual. It is less likely for individuals of any age to live alone post-TBI, so caretakers or living partners must be educated on the consequences of ongoing substance use, such as increased risk for recurrent injury, lowered alcohol tolerance and seizure thresholds. It is advisable to make the discharge environment alcohol and substance-free. Co-dependency issues must be addressed and confronted directly. Hurt and colleagues recommend equally intense treatment of the older individual with alcoholism as the younger one. Follow-up of their cohort 2 to 11 years post-inpatient treatment showed that 25 percent were able to remain sober, 41 percent had returned to alcohol use, and 32 percent were dead, nearly one-half from alcohol-related causes (69).

### **Continence**

*Bladder* Normal aging affects bladder function in the following ways: 1) prostate hypertrophy in men with

relative bladder outlet obstruction and diminished capacity with symptoms of urinary frequency, hesitancy and/or diminished stream; 2) pelvic relaxation in women from uterine prolapse or cystocele resulting in intermittent stress incontinence; 3) decreased bladder capacity with urinary frequency; and 4) decreased capability to suppress bladder contractions at low volumes resulting in urgency (74). Individuals with TBI are typically incontinent with urinary frequency because of inability to sense bladder fullness and/or suppress the pontine micturition center (75). Increased frequency may be a symptom of urinary tract infection. Medications that commonly affect bladder emptying include those with anticholinergic side effects, calcium channel blockers, antihistamines and narcotics. Bowel impaction, prostatic hypertrophy, and peripheral neuropathy may cause relative obstruction or the tendency to retain urine, which may also lead to infection. Incontinence may also occur with normal bladder functioning if the individual has impaired mobility or self-care skills that prevent efficient use of a toilet or urinal. Assessment of pre-injury voiding patterns is helpful in discerning any underlying pathology, independent of the effects of the TBI.

The first step in re-assessing current bladder function is removal of the indwelling bladder catheter or diaper that invariably accompanies the individual with TBI from acute care or skilled nursing settings. Elimination of medications that interfere with bladder physiology as mentioned above permit adequate baseline performance. A timed voiding schedule using a bedside commode or toilet in sitting or standing position can then facilitate regular opportunities for bladder emptying. It is difficult for many able-bodied individuals to have adequate bladder emptying in bed. Measurement of the post void residual urine volume (PVR), either by portable bladder ultrasound or by one-time bladder catheterization, can quantify the degree of emptying. If the PVR is less than 50 cc, then further measurements are unnecessary; between 50–100 cc, it is advisable to perform several repeated measurements to insure that residual volumes do not put the individual at risk for infection. Larger PVRs greater than 30% of total bladder volume (spontaneous void plus PVR) may indicate mechanical outlet obstruction, poor detrusor contraction or incomplete sphincter relaxation. Common conditions associated with this pattern are prostatic hypertrophy, peripheral neuropathy, or cystocele. Alpha-receptor blockers such as alfuzocin, doxazosin, terazosin or tamsulosin may aid in allowing the individual to relax the internal and external sphincters.

Timed voiding schedules and medication use can be re-evaluated as the individual's self-awareness, mobility and safety with toileting techniques improve. These interventions are often necessary for several weeks, but their usage can avoid the morbidity associated with diaper, indwelling or even condom catheter use.

**Bowel** Patients' bowel routines are typically disrupted during hospitalization for trauma and are a low priority in acute care settings. In older individuals, such disruption can become a preoccupation unless it is properly addressed. Fecal incontinence is prevalent in 68% of individuals with TBI on acute rehabilitation admission, 12.4% at rehabilitation discharge and 5.2% at one-year follow-up. Among other variables age is associated with incontinence at discharge and one-year post TBI (76).

Ascertaining a person's pre-injury bowel routine is the first step in establishing goals. Dietary changes, immobility and narcotic use for pain management are the most common causes for constipation in this population (43). However, until safe swallowing, mobility and routine gastrointestinal motility are re-established, interim measures are usually necessary.

For suspected fecal impaction which can present as loose incontinent stool leaking around the impacted area, one-time laxative, bowel stimulant and /or suppository often relieves the problem. Stool softeners or fiber may be advisable for some time because of ongoing therapeutic measures for pain management or iron replacement.

Diarrhea or loose stool is common with antibiotic usage and some enteral formulas. Infectious causes of diarrhea, especially *Clostridium difficile* should be treated. Fiber-containing enteral formulas or lactobacillus supplements can improve stool consistency. Bolus feedings encourage the gastrocolic reflex and more regular bowel evacuation patterns. Once an acceptable pattern has been established, interventions can be weaned serially to determine which if any are still necessary (77).

## Sensory Health

**Vision** Normal aging is associated with changes in visual acuity and refractive power, decrements in extraocular motion, increases in intraocular pressure, decreased tear secretion, and decreased corneal and lens function (43). Most older individuals use corrective lenses for reading and many for distance vision as well. Corrective lenses are often lost or broken during the acute traumatic event and not used during acute hospitalization. Decreased visual function can add to perceptual deficits and confusional states. Easily correctable visual problems, especially the resumption of glaucoma medication or finding a useful pair of corrective lenses can aid the rehabilitation process.

**Hearing** Normal aging is associated with loss of sensitivity and signal distortion of higher frequencies, difficulty localizing signals needed for dual ear listening, and difficulty in understanding speech in unfavorable listening conditions. Life-long noise exposure, middle ear and vascular disease can also affect hearing. Presbycusis, affecting 60% of individuals over the age of 65, is a progressive sensorineural hearing loss separate from all of the

above (43). With trauma, middle ear ossicles or cranial nerve VIII can be selectively damaged, especially with basilar skull fractures. The use of pre-injury prescribed hearing aids is challenging because the injured individual is often the only one familiar with their adjustment. Yet accurate communication is critical in helping individuals progress through their acute confusional state and communicate with caretakers and helping professionals. Until hearing aid use can be reestablished, written communication, direct eye contact to facilitate lip reading, gestural communication, and an environment without extraneous noise are helpful alternatives.

*Smell* Anosmia is probably the most frequent cranial nerve and sensory loss specifically associated with TBI (78, 79). It may result in decreased appetite while in the hospital. In the home environment it may impair the individual's ability to detect burning objects promptly. Presence of smoke detectors in the discharge environment is therefore part of the evaluation that should accompany home safety assessment with caregivers.

*Taste* Normal aging is accompanied by loss of lingual papillae, decreased saliva volume, and a relative decrement of taste acuity (43). It is relatively easy to test the basic elements of salty, bitter, sweet and sour tastes. It is best to have visitors bring in the patient's favorite foods when it is deemed safe for swallowing to fully ascertain whether the changes in taste or smell are going to affect the patient's appetite.

*Touch, Vibration and Joint Position Sense* Vibratory sense diminishes with age. Conditions associated with peripheral neuropathy are also more frequent in older individuals, although acute peripheral nerve, brachial and lumbosacral plexopathies are less frequent concomitant injuries in older adults. Reversible etiologies of peripheral neuropathy such as vitamin deficiencies, thyroid abnormalities, and neurotoxic medications should be identified and treated. Less reversible causes such as diabetes mellitus, alcoholism, uremia, HIV and syphilis are still worth identifying so that progressive neuropathy may be managed with better glucose control, alcohol abstinence or definitive treatment of the underlying condition. Compensation techniques, assistive devices for mobility and self-care, and adequate lighting may help the individual adapt to these impairments.

### Behavior and Cognition

Dementia affects 3 to 11% of community-dwelling adults over age 65, 20 to 50% of those older than 85, and nearly 60% of centenarians. Traumatic brain injury is one of the multiple etiologies of dementia (80). Therefore, it is important to ascertain an individual's pre-injury motivation, behavior and mental capacity in order to have reasonable expectations for cognitive recovery from their TBI.

The typical recovery pattern for older adults with TBI is not appreciably different than younger individuals. It includes an initial period of diminished arousal, followed by hyperarousal and culminating in return to a new baseline level of arousal, that may differ from pre-injury function. Goldstein and Levin compared 22 individuals with TBI over age 50 living in the community with age, gender and education-matched controls and found that those with TBI had more difficulty with verbal and non-verbal learning, expressive language, executive functioning, and depression (81). The treatment team can influence a safe transition through the various levels of recovery by preventing secondary injury, treating concomitant symptoms and illnesses, targeting pharmacological interventions, and engineering the environment. Facilitating transition to the most familiar discharge setting and use of familiar calendars and memory aids can help with motivation and compensating for these deficits.

### Attention

Decreased arousal and attention are common after DAI, hypoxic ischemic injury and dorsal lateral or deep frontal lobe injury. Hypoarousal is characterized by difficulty staying awake despite adequate sleep and appropriate stimulation. Hypoattention is characterized by inability to attend to conversation or self-care tasks with adequate alertness. Either deficit can interfere with progress in recovery. Management techniques include normalizing sleep-wake cycles, establishing routine up-down schedules, minimizing medications with sedating side effects, and control of distractions in the environment. Attention deficits can be treated safely in the older adult without concomitant coronary artery disease with methylphenidate; the short-acting preparation will yield results within several days (82). Carbidopa/levodopa may be useful if inattention is accompanied by bradykinesia and rigidity, with results apparent within 1–2 weeks of initiating therapy. Amantadine, modafenil, and SSRI's are usually safe medications but have longer onset of action (83).

### Agitation

Restlessness and agitation occur in approximately one-third of individuals with moderate to severe TBI. They interfere with safety and participation in activities of daily living and especially rehabilitation programs (84, 85). The Agitated Behavior Scale and checklists that quantify specific behaviors are very useful for monitoring agitation over time (86, 87). Agitated individuals with TBI are more likely to have psychological adjustment difficulties, require supervision or institutional placement after discharge (88). Management strategies include behavioral plans, environmental modifications using cubicle or enclosure beds, structured therapy sessions with co-treatment, 1 to 1 attendant

care, appropriate pain control, and medications for specific targeted behaviors (89). Commonly used medications include non-sedating anticonvulsants, tricyclic or heterocyclic antidepressants, amantadine, beta-blockers, and atypical antipsychotics. Benzodiazepines are generally thought to be safe medications, but can cause paradoxical agitation or increase levels of confusion and amnesia particularly when the sedative effect wanes (90).

### Alteration in Mood and Sleep

Depression occurs in 20–70% of individuals during the first 2 years after TBI; studies do not stress that age is a risk factor for depression (91). In the general population, anxiety and major depression are less common in older than in younger individuals (92). Severity of injury and level of physical disability do not correlate with frequency or severity of depression (93).

Normalizing sleep-wake cycles is as important in managing mood disorders as it is in disorders of arousal and attention. Contributing factors to insomnia include interrupted sleep by hospital personnel or other patients, persistent effects of sedating medications, pain, and poor sleep hygiene. The latter can be addressed with a balanced activity schedule during the day, scheduled rest periods, minimizing nighttime disturbances, and having a daytime and evening routine (94). Low doses of eszopiclone, zolpidem or zaleplon can be useful for helping to initiate sleep for 3–4 weeks. If longer-term usage is anticipated, trazodone may be a better choice. Diphenhydramine and hydroxyzine are second-line agents, but should be used with caution because they may also cause urinary retention. Benzodiazepines frequently cause paradoxical reactions in the elderly, and tricyclic antidepressants are associated with postural hypotension and urinary retention that are poorly tolerated.

Psychological counseling is appropriate for the majority of individuals. Incorporating children and grandchildren into therapeutic and recreational activities can be most therapeutic. Early therapeutic outings to assess function in the home and community can enhance motivation. Methylphenidate is a short-acting agent that improves both arousal and attention and may assist in alleviating depressive symptoms. SSRI's are safe and common first-line antidepressant medications for older individuals because of their favorable side-effect profile. Onset of action is 3–6 weeks. Medication interactions and side-effect profiles are most important in this age group given concurrent morbidities (90).

### Safety Judgment

Pre-morbid or newly acquired deficits in cognition, strength, balance and sensation often challenge an individual's safety in the discharge environment. Awareness

and adjustment to these deficits determines the level of supervision needed at home (6). Prevention of future injury secondary to falls or wandering often requires added caretakers and resources in the discharge environment. See above section on Age and Outcome regarding supervision needs over time.

### Competence and Capacity

The acute and chronic cognitive, behavioral and communication deficits described above may affect capabilities for self-determination for health care and financial decisions in anyone with a TBI. *Competence* is legal term pertaining to an individual's right to self-determination; *capacity* is a medical term that pertains to the physical and cognitive abilities to convey and carry out one's wishes. An interdisciplinary evaluation by an appropriate and interested physician, psychologist, occupational therapist and / or speech and language pathologist is recommended to provide a comprehensive assessment that includes topographical and verbal orientation, money management, communication and reasoning skills (95). Older individuals are more likely to have a pre-existing durable power of attorney than younger individuals. If available, health care and even financial decisions can be facilitated. If not, each state or province has different guidelines regarding who can help the individual with TBI make such decisions. Court-appointed temporary and permanent conservators may be necessary to facilitate ongoing medical and financial decisions.

### Sexuality

As a consequence of common beliefs in our society, sexuality is often ignored in older adults. This tendency frequently persists in rehabilitation settings, particularly in the face of new disabilities. Sexuality encompasses a sense of self, the capacity to show affection, love and maintain relationships, and knowledge of the social context of sexual behavior and gender roles. In early stages of recovery from TBI, sexual comments may be less tolerated in older than younger individuals. Physiologic changes in vaginal mucosa, erectile and orgasmic performance often occur in normal aging. Changes in sexual desire in either direction can occur; there may be decreased interest and desire or an egocentric, impulsive, or disinhibited behavior pattern. Therefore, it is just as important to screen for sexual and relationship concerns in older individuals. Because of the multi-faceted nature of sexual relationships, techniques to enhance overall communication and interaction skills are most therapeutic (96). Sildenafil, tadalafil, and vardenafil, while effective for erectile dysfunction commonly encountered after TBI, is often contraindicated in older adults due to concomitant coronary artery disease and hypertension.

### Self-Care

Standard rehabilitation principles to recover self-care abilities are just as effective in the older adult with TBI. They may have comparable difficulty being motivated to learn “splinter skills” that are a small portion of a task, such as range of motion exercises alone. More whole task oriented therapy is better accepted. Learning an individual’s pre-injury habits and routines is vital to organizing relevant therapy. It is also important to secure some familiar clothing and grooming utensils, incorporating them into familiar daily routines in the hospital setting. Typical adaptive equipment recommendations include built-up or weighted utensils to accommodate upper body weakness, loss of dexterity and joint limitations; long-handled devices and reachers to accommodate difficulties with trunk balance and flexibility; bathroom safety aids (grab bars, tub or shower benches, hand-held shower heads, raised toilet seats or commode chairs) to compensate for decreased balance and strength. Home management skills, both physical performance as well as organization, are likely to require modification.

### Mobility

Challenges to safe ambulation in the older adult include learning how to accommodate for alterations in vision, peripheral or central sensation, balance, strength, and overall endurance. Chronic arthritis, joint and muscle stiffness are more common in the elderly. Household mobility may be facilitated with a home evaluation by members of the rehabilitation team to assess architectural barriers (doorways, stairs, floor coverings), furniture arrangement, adequacy of natural and artificial lighting as well as training for caregivers in safe mobility practices in the discharge environment.

Community mobility goals include the ability to get from place to place with route-finding and bodily transport and negotiating different terrains such as pavement, grass, curbs and stairs. Public transportation for individuals with disabilities is becoming increasingly available throughout the world, with various levels of governmental support. Focusing on familiar routes and routines, then gradually progressing to finding one’s way in new surroundings is a typical sequence for increasing community mobility skills.

### Driving

Safe driving after a TBI must take into account the older adult’s pre-injury capabilities and new impairments. Some jurisdictions require health care practitioners to report to public health authorities or the department of motor vehicles (DMV) physical or cognitive conditions that may alter one’s driving safety. The DMV’s response also varies

by location, even within the same state. Some states or provinces may revoke a driver’s license after being reported by a health care practitioner. Interviews and more rigorous testing procedures may be given to those with seizures, cognitive or motor deficits (97, 98). Comprehensive driving evaluations may be helpful, although third-party commercial or government insurance funding is rarely available, unless the disability is the result of a work or military service-related injury. Cognitive and physical testing may rule out an individual’s inability to drive if there are no obvious deficits in strength, sensation or vision. No test replaces an actual on-the-road evaluation in order to insure driving safety (99, 100).

### Recreation and Vocation

A thorough survey of an older adult’s pre-injury recreational pursuits is necessary in order to explore options post-TBI. Sedentary activities can usually be resumed with minor modifications, if any. Socialization opportunities may have been the primary leisure activity and is appropriate afterwards, perhaps minus any accompanying substance use. Resumption of group activities in the rehabilitation setting and community settings is important to minimize feelings of isolation.

Return to work rates are poor for older adults after TBI. Realistic goals need to be established with appropriate supports in the work place. Often early retirement or part-time volunteer work is necessary when an individual cannot return to their workplace (101).

### Case Example

AR is a 73-year-old married man who fell down a stairwell at a hotel party while on vacation, landing on his head. He lost consciousness at the scene, was initially unable to move his legs, and had significant scalp lacerations. In the ER, GCS was 12 and he began to move his legs. CT scan of his head revealed occipital and basilar skull fractures, multiple cerebral contusions, subdural and subarachnoid hemorrhages. None of these required surgical intervention. His associated injuries included right hemothorax and pulmonary contusions, grade 1 liver laceration, cervical 5–7 vertebral body fractures, thoracic, lumbar and sacral fractures, and bilateral pubic rami fractures. His past medical history included a cardiomyopathy, probably secondary to alcoholism, with 30 to 35% ejection fraction and an episode of ventricular tachycardia in the last year, gout, and colon cancer 10 years previously. He has an MBA, is retired as president of a construction company and has lived with his wife of 50 years in a 2-story home. His hobbies are playing tennis and traveling.

He was initially intubated for airway control and underwent tracheostomy, T3 – T12 laminectomies, rod- and bone graft; C3-7 posterior stabilization and



lumbosacral stabilization. He was extubated and started following commands consistently 3 weeks post-injury. He required no intracranial surgery.

Four weeks post-injury he was transported to a hospital in his community via air ambulance. Occupational, physical and speech therapies were initiated. Within 2 days he needed to be mechanically ventilated again due to exacerbation of congestive heart failure and was gradually weaned from the ventilator over 2 weeks while his cardiac medications were re-adjusted.

At 6 weeks post injury he was admitted to acute rehabilitation, dependent in all areas of mobility and self-care at Rancho level 5. His speech was fluent and he was oriented to person, city, and that he was in the hospital because of a fall. Upper extremity strength was symmetrical and grade 3/5 strength at the shoulders, 4/5 at the elbows, wrists and hands with wasting of his interossei but good dexterity. Lower extremities were symmetrical except at the ankles with grade 1/5 strength at the hips, 2/5 at the knees and left ankle, 1/5 at the right ankle. Sensory exam showed a stocking distribution of loss to all modalities below the ankles. His tracheostomy was being plugged for most of the day.

He emerged from posttraumatic amnesia 2 months post-injury while watching Wimbledon tennis matches on TV, which aided his orientation to time and date. A nerve conduction study showed moderate severe peripheral polyneuropathy with an additional right peroneal nerve injury. He had near syncopal episodes whenever he removed his elastic support hose with SBP as low as 70 mm Hg. After 4½ weeks of acute rehabilitation, he required extra time but was independent in eating, grooming, and using a urinal. He was supervised for donning a shirt and required less than 25% assistance for dressing and washing his lower body, transfers to unlevel surfaces using a sliding board. He could propel his wheelchair 100 feet before tiring and started walking using the parallel bars and a walker. He was discharged home with home health therapy for 3 weeks followed by outpatient therapy for 2 months. He progressed to using a front-wheeled walker or cane with a right ankle foot orthosis for household and short-distance ambulation. Within several months of discharge he was able to resume management of his financial affairs and even go on a cruise with his wife and friends. His most bothersome ongoing symptom is pain in his feet and legs from his polyneuropathy. One year later he still hopes to play tennis again.

AR had several poor prognostic signs, including previous symptomatic cardiomyopathy, multiple fractures requiring surgery and prolonged PTA. However, he received excellent medical and rehabilitative care, had good family support and the will to not just survive but make the most of his capabilities. His recovery illustrates how a coordinated system of care can produce favorable outcome despite many potential pitfalls.

### **TBI, Apolipoprotein E4 and Dementia**

Apolipoprotein E4 (APOE-4) is a lipid transporter in the brain and cerebrospinal fluid (102). and is believed to play a role in the inflammatory response and neuronal repair following trauma. It is the product of a single gene and has been related to age-related cognitive impairment, decreased synapse-neuron ratio, increased susceptibility to neurotoxins, and hippocampal atrophy (103). Individuals with a history of TBI and apolipoprotein E4 (APOE 4) allele had 10 times the risk of developing Alzheimer's disease compared with 2 times the risk with APOE 4 alone and no increased risk with TBI alone (104). Nicoll and colleagues examined the brains of 90 individuals who died of severe TBI. All individuals homozygous for APOE 4 had beta amyloid plaques (BAP); overall, 52% of those with BAP had at least one APOE 4 allele while only 16% of those with no BAP had APOE 4 (105). Teasdale and colleagues analyzed 89 individuals with TBI with and without apoE-4 allele. 57% of those with the allele versus 27% of those without had 6-month outcome of death, vegetative state or severe disability (106). The presence of APOE 4 alleles, especially in the homozygous condition appear to be associated with worse outcome after TBI. Individuals with APOE 4 allele also have associated poor outcome after spontaneous non-aneurysmal intracerebral hemorrhage, amyloid angiopathy, and subarachnoid hemorrhage(103). Nearly all the above studies have been performed on individuals of western European genetic backgrounds and environments, so it is difficult to generalize the association across races and environments (107, 108).

### **AGING WITH TBI**

Conflicting data exist in the literature regarding aging and TBI. Amongst the published studies, various issues were examined including: time of onset of Alzheimer's Disease (AD), long-term neuropsychological outcome, incidence and causes of mood disorders, re-hospitalization, morbidity, mortality, as well as psychosocial outcome and satisfaction with life.

### **Alzheimer's Disease**

In a population-based cohort who acquired their TBI between 1935–1984, Nemetz et al found no greater incidence in the number of individuals with Alzheimer's disease, but a earlier onset, 10 years versus 18 years, suggesting that TBI may reduce the time of onset of dementia in those already at risk for Alzheimer's disease (108).

### **Neuropsychological impairment**

Increasing age is associated with greater neuropsychological impairment (e.g. diminished memory, slower

processing speed), but it is unclear whether it is the case for aging with a brain injury.

Johnstone et al. studied 279 individuals with a TBI over a 4-year period. They used age-based normative data to determine the decline in cognition compared to pre-injury levels for different age groups. They found that neuropsychological impairments noted in older individuals with a TBI are typical of changes with normal aging (109). Millis and colleagues looked at neuropsychological recovery from 1 year to 5 years after injury. They studied 182 persons with mild to severe TBI. Digits forward and backward, logical memory I and II, token test, controlled oral word association test, symbol digit modalities test, trail making test, Rey auditory verbal learning test, visual form discrimination, block design, Wisconsin card sorting test, and grooved peg board were used as neuropsychological data. Improvement from 1 year after injury to 5 years was variable. On test measures, 22.2% improved, 15.2% declined and 62.2% were unchanged. Patients showing improvement were most likely to have changed on measures of cognitive speed, visual spatial construction, and verbal memory. Decline was most pronounced on measures requiring rapid performance and cognitive flexibility (110).

### Mood Disorders

Little is known about the long-term risk of depression after TBI. Holsinger and colleagues compared the prevalence of depression 50 years after injury in 520 World War II veterans with and 1198 veterans without TBI. Head-injured veterans were more likely to report major depression in subsequent years and were more often currently depressed.

Lifetime prevalence of major depression in the head injured group was 18.5% versus 13.4% with no TBI. Current depression was detected in 11.2% of the veterans with brain injury versus 8.5% of those without (111). Thomsen found 20% incidence of psychotic behavior with onset 3 months to 6 years post injury; symptomatic memory problems in 75%, personality and emotional changes in 65%, concentration and mental slowness in 53% and loss of social contact in 68% of 40 individuals between 10–15 years post severe TBI (112).

### Hospitalization

Regarding health issues after TBI, Marwitz and colleagues investigated the incidence and etiology of rehospitalization 1 and 5 years after injury in 799 individuals. The annual incidence and of rehospitalization ranged from 22.9% 1 year after injury to 17.0% 5 years after injury. At 5 years after injury, general health maintenance was the most common reason for admission (36%) followed by seizures (18.7%), psychiatric (16%) and orthopedic (13.3%) etiologies (113).

### Psychosocial Outcome

Corrigan JD and colleagues examined outcomes in the first 5 years after TBI. They studied 95 adults 6 months to 5 years after inpatient rehabilitation for a TBI. Their outcomes measures included the following: Functional Independence Measure (FIM), Sickness Impact Profile (SIP), Medical Outcome survey Short Form-36 (SF-36), Community Integration Questionnaire (CIQ) and Satisfaction with Life Scale (SWLS). Outcomes 5 years after discharge showed improvement with most change occurring within the first 2 years (114).

A study by Mazaux and colleagues followed 79 individuals with TBI by phone interview 9 years after injury to assess their late functional outcome and satisfaction with life. Sixty-five to 85% of individuals were independent in activities of daily living (ADL) whereas only 35–55% of persons with TBI were independent with social interaction. Most people were satisfied with their level of autonomy (67%), family life (66%) and financial status (41%). Dissatisfaction was expressed regarding leisure activities (36%), vocational adjustment (28%) and sexual function (32%) (115).

The TBI National Data Base has 178 subjects comprising a range of age 16 to 80 who have acute rehabilitation discharge, 1-year and 10-year follow-up data. Using a global functioning measure such as the DRS, there is evidence that individuals achieve overall improvement in capabilities and independence over time: scores improve from rehabilitation discharge (5.53, SD 2.87) to 1-year (2.93, SD 2.82) and 10-years (2.14, SD 2.65) post TBI. Competitive employment increases from 22.5 to 29.5% between 1 and 10-years post TBI, and there is also a trend towards retirement. Whether that is occurring for just age-related or medically-related reasons is not defined in the database. Return to school on at least a part-time basis is typical at 1-year post injury but not at 10 years. With this cohort there is also a bias with regards to their ability to be followed over time. Although there is no control group, the overall capabilities and employment demonstrated is less than the general population (12) (see Table 21-2). These and other data above indicate that improvement in social status and achievement can continue over time even as the basic neurological recovery has stabilized.

### Mortality

Shavelle RM and collaborators examined causes of death more than one year after TBI. Mortality rate was elevated for circulatory diseases, respiratory diseases, choking/suffocation, and seizures. Mortality was higher between 1 and 5 years post-injury than after 5 years and was strongly related to reduced mobility. The markedly elevated mortality in those with reduced mobility is not

**TABLE 21-2**  
*Productive Activity Before and After TBI (12)*

	PRE-INJURY	1 YEAR POST-INJURY	10 YEARS POST-INJURY
Competitive Employment	59.9%	22.5%	29.5%
Full-time student	9.0%	4.0%	0%
Part-time student	0.6%	5.8%	0.6%
Homemaker	1.1%	2.9%	2.9%
Retired (age)	4.5%	5.8%	29.5%
Unemployed	24.3%	53.8%	28.3%
Other	0.6%	5.2%	9.2%

surprising, as a sedentary lifestyle is known to be associated with increased mortality risk, especially because of diseases of the circulatory system (114).

## CONCLUSION

Traumatic brain injury in the older adult occurs primarily as a result of falls, pedestrian versus motor vehicle collisions, and low- to moderate-speed motor vehicle crashes. The aging of the population in industrialized countries has resulted in an increasing incidence and prevalence of TBI in this age group and particularly among older women. Cerebral pathology in these injuries tends to be more focal with SDH's and contusions. Injuries from motor vehicle crashes also result in DAI. Severe injuries are less commonly survived, but individuals who do survive can have favorable functional outcomes.

Caring for the older individual with TBI requires employing a combination of the principles of geriatric medicine and brain injury rehabilitation, with close attention to the timing, setting and intensity of therapeutic interventions. Models of care need to adapt to the unique needs of the older adult.

Older individuals with TBI usually require more time to recover cognitively and physically than younger individuals. Removal or simplification of medication regimens is usually more efficacious than adding new ones. Therapeutic interventions must be tailored to the individual's and family's needs in their specific post-discharge environment with early training of caregivers and environmental modifications for safety (41, 77). Aging with TBI may progress more rapidly than aging without such injuries, particularly in some individuals with genetic predisposition. Most individuals improve gradually over time with regards to their physical and cognitive functioning,

frequency of rehospitalization and employment. However, as a group individuals with TBI have more medical and psychosocial challenges than those who were never injured.

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# 22

## Mild TBI

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### INTRODUCTION

Mild traumatic brain injuries are common. Bazarian and colleagues (1) reported that 56/100,000 people are evaluated in the emergency department each year for an *isolated* mild traumatic brain injury (MTBI). Sosin et al. (2), based on the National Health Interview Survey in 1991, estimated that 1.5 million Americans suffer a traumatic brain injury each year (i.e., 618/100,000), with the vast majority being mild in severity. This, of course, is much higher than previous estimates based on hospital admissions because most people who sustain a mild traumatic brain injury are not evaluated in the emergency department or admitted to the hospital (2). For example, mild injuries, such as concussions in sport, are very common. In a recent study, 30 percent of high school football players reported at least one previous concussion; 15 percent reported that they had experienced a concussion during the current football season (3).

For most people, MTBIs are self-limiting and generally follow a predictable course. Permanent cognitive, psychological, or psychosocial problems due to the biological effects of this injury are relatively uncommon in trauma patients and rare in athletes (see Refs. 4–9 for recent comprehensive reviews). Slow or incomplete recovery from MTBI is poorly understood, despite decades of research.

The purpose of this chapter is to provide a comprehensive overview of MTBI. The discussion is divided into the following 11 sections: (a) terminology, (b) pathoanatomy and pathophysiology, (c) S-100B as a marker for injury and predictor of outcome, (d) neuropsychological outcome, (e) early intervention, (f) return to work, (g) depression, (h) post-traumatic stress disorder, (i) risk for Alzheimer's disease, (j) persistent post-concussion syndrome, and (k) conclusions. This chapter does not provide a detailed review of concussions in sports or the differential diagnosis of the persistent post-concussion syndrome. Two chapters in this book are devoted to those topics.

### TERMINOLOGY

There is no universally agreed-upon definition of MTBI. However, the most commonly used definitions are very similar. The maximum duration of unconsciousness, for example, has been 20, 30, or 60 min or less in various studies. The duration of post-traumatic amnesia has been 60 min or less in some studies, and less than 24 hr in others (see Ref. 10 for a review).

Some researchers have differentiated *complicated* from *uncomplicated* MTBI (11). A complicated MTBI is diagnosed if the person has a Glasgow Coma Scale (GCS)

score of 13–15 but shows some brain abnormality (e.g., edema, hematoma, or contusion) on a CT-scan. Skull fractures were also considered characteristic of complicated injuries in Williams et al., but fractures have been investigated separately by other researchers. Williams and colleagues noted that patients with complicated MTBIs are more likely to have persistent cognitive and psychological symptoms, and their 6-month recovery pattern is more similar to persons with moderate head injuries. Complicated MTBIs are discussed in detail in the pathoanatomy/pathophysiology and the neuropsychological outcome sections of this chapter.

The uncomplicated MTBI is characterized by having no intracranial abnormality or skull fracture, with all other severity criteria in the mild range. Notably, there are several subtypes of injuries; the severity of injury, types of symptoms, and course of recovery can vary in relation to these subtypes. For example, it is assumed (although not well studied) that the person who is “dazed” and may have lost consciousness for a few seconds is much more likely to experience a rapid and complete recovery than a person who is unconscious for 20 min and has post-traumatic amnesia for 12 hr.

An interdisciplinary subcommittee published a definition of MTBI that was designed to clarify classification and improve cross-study comparisons. The definition was developed by the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (12). This definition is provided in Table 22-1.

**TABLE 22-1**  
**ACRM (12) Definition of Mild Traumatic Brain Injury**

A traumatically induced physiological disruption of brain function, as manifested by at least one of the following:

1. any loss of consciousness;
2. any loss of memory for events immediately before or after the accident;
3. any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused); and
4. focal neurological deficit(s) that may or may not be transient; but where the severity of the injury does not exceed the following:
  - loss of consciousness of approximately 30 min or less;
  - after 30 minutes, an initial Glasgow Coma Scale (GCS) of 13–15; and
  - posttraumatic amnesia (PTA) not greater than 24 hr.

*Note:* A better conjunction after point #3 should have been “or” as opposed to “and”.

This article was intended to provide a standard definition, established by consensus of a committee, to facilitate communication regarding MTBI in research and in clinical practice. The focus of the article was on how to determine whether an MTBI has occurred, by establishing injury severity criteria. The committee definition is widely cited in clinical practice and research. A major limitation to this definition, however, is the inclusion of a broad range of injury severity. This definition ranges from a *trivial* injury involving seconds of confusion, to a complicated MTBI involving 20–30 min of unconsciousness, several hours of post-traumatic amnesia, and a focal contusion.

In a report to the U.S. Congress in 2003, a working group provided the conceptual definition of MTBI set out in Table 22-2 (13). This Centers for Disease Control (CDC) working group also proposed limited criteria for identifying MTBI-related impairment, functional limitations, disability, and persistent symptoms in population-based surveys. These criteria are set out in Table 22-3.

The CDC working group acknowledged that this definition does not define subtypes of MTBIs within the

**TABLE 22-2**  
**National Center for Injury Prevention and Control (13) Conceptual Definition of MTBI**

The conceptual definition of MTBI is an injury to the head as a result of blunt trauma or acceleration or deceleration forces that result in *one or more* of the conditions listed below.

Any period of observed or self-reported:

- Transient confusion, disorientation, or impaired consciousness;
- Dysfunction of memory around the time of injury;
- Loss of consciousness lasting less than 30 min.
- Observed signs of neurological or neuropsychological dysfunction, such as:
  - Seizures acutely following injury to the head;
  - Among infants and very young children: irritability, lethargy, or vomiting following head injury;
  - Symptoms among older children and adults such as headache, dizziness, irritability, fatigue or poor concentration, when identified soon after injury, can be used to support the diagnosis of mild TBI, but cannot be used to make the diagnosis in the absence of loss of consciousness or altered consciousness. Research may provide additional guidance in this area.

More severe brain injuries were excluded from the definition of MTBI and include *one or more* of the following conditions attributable to the injury:

- Loss of consciousness lasting longer than 30 minutes;
- Post-traumatic amnesia lasting longer than 24 hr;
- Penetrating craniocerebral injury.

spectrum of the injury, and that researchers might continue to establish the importance of subtypes. The working group noted that the presence of an intracranial abnormality was one injury characteristic that should routinely be reported when available.

**TABLE 22-3**

***CDC Working Group Limited Criteria for Identifying MTBI-Related Impairment, Functional Limitation, Disability, and Persistent Symptoms in Population-Based Surveys [National Center For Injury Prevention and Control (13)]***

Current symptoms reported consequent to MTBI not present before injury or those made worse in severity or frequency by the MTBI:

- Problems with memory
- Problems with concentration
- Problems with emotional control
- Headaches
- Fatigue
- Irritability
- Dizziness
- Blurred vision
- Seizures

Current limitations in functional status reported consequent to MTBI:

- Basic activities of daily living (e.g., personal care, ambulation, travel)
- Major activities (e.g., work, school, homemaking)
- Leisure and recreation
- Social integration
- Financial independence

The CDC working group cautioned that most of these symptoms and limitations in Table 22-3 are associated with many other conditions, not just MTBI. The working group expressed concern regarding the limitations associated with the lack of specificity of the symptoms and functional limitations, but thought that these problems could be partially mitigated by the careful selection of appropriate comparison groups, cautious interpretation of findings, and by evaluating pre- and post-injury symptom reporting.

Under the auspices of the European Federation of Neurological Sciences, a task force published a classification system for MTBI that could be used to guide initial *management decisions* for emergency physicians (e.g., whether or not to undergo brain CT scanning). The EFNS subclassifications (14) for MTBI are presented in Table 22-4.

In 2004, a comprehensive review of the literature on MTBI was published in a series of articles in the *Journal of Rehabilitation Medicine* (e.g., 5, 15–18). The WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury provided the following definition.

MTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: (i) one or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (ii) Glasgow Coma Scale score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare. These manifestations of MTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g. systemic

**TABLE 22-4**

***EFNS Classification Guidelines (14) for the Acute Management of MTBI***

<b>INJURY SEVERITY CLASSIFICATION</b>	<b>GLASGOW COMA SCALE</b>	<b>LOSS OF CONSCIOUSNESS</b>	<b>POST-TRAUMATIC AMNESIA</b>	<b>RISK FACTORS</b>
Category 0	15	None	None	None
Category 1	15	< 30 minutes	< 1 hour	None
Category 2	15	< 30 minutes	< 1 hour	Yes
Category 3	13–14	< 30 minutes	< 1 hour	Yes or No

Risk factors for intracranial complications following MTBI: (1) unclear or ambiguous accident history, (2) continued post-traumatic amnesia, (3) retrograde amnesia longer than 30 min, (4) trauma above the clavicles including clinical signs of skull fracture, (4) severe headache, (5) vomiting, (6) focal neurological deficit, (7) seizure, (8) age < 2 yr, (9) age > 60 yr, (10) coagulation disorders, (11) high-energy accident, (12) intoxication with alcohol/drugs.

*Note:* The subclassifications were proposed to facilitate initial management decisions. Category 0 was conceptualized as a head injury with no traumatic brain injury. “According to Advanced Trauma Life Support principles, a high-energy (vehicle) accident is defined as initial speed >64 km/h, major auto-deformity, intrusion into passenger compartment >30 cm, extrication time from vehicle >20 min, falls >6 m, roll over, auto-pedestrian accidents, or motorcycle crash >32 km/h or with separation of rider and bike (406, 407)” (p. 210).



injuries, facial injuries, or intubation), caused by other problems (e.g. psychological trauma, language barrier, or coexisting medical conditions) or caused by penetrating craniocerebral injury” (page 115; 10)

Without question, MTBIs can be characterized by damage to the structure and certainly the function of the brain. A minority of patients with MTBIs have visible abnormalities on CT or MRI conducted on the day-of-injury or within the first two weeks post injury. The mainstream definitions of MTBI include patients with these visible structural abnormalities. For the most part, however, the pathophysiology of MTBI is neurometabolic. The pathoanatomy and pathophysiology of MTBI are discussed in the next section.

### **PATHOANATOMY AND PATHOPHYSIOLOGY**

MTBIs can be characterized by damage to the structure of the brain. Clinicians and researchers often emphasize that most patients with MTBIs have normal structural neuroimaging studies; this is certainly true. However, a substantial minority of patients have day-of-injury abnormalities visible on CT. Approximately 7 to 20 percent of consecutive patients presenting to the emergency room<sup>1</sup> with an MTBI have bleeding, bruising, or swelling on day-of-injury computed tomography (17, 19–24). Borg and colleagues conducted a comprehensive review of this literature and concluded that the estimated prevalence of CT abnormalities of patients seen in the hospital was 5 percent for those with GCS scores of 15 and 30 percent or more for those with GCS scores of 13 (17). Not surprisingly, patients with macroscopic abnormalities on their day-of-injury CT have microscopic damage or dysfunction as well, as reported in both the animal and human literature. For example, in animal (25) and human studies (26–28) there appear to be observable changes in the vicinity of brain contusions that are related to neuronal metabolic pathophysiology (most notably with *N*-acetylaspartate, creatine and phosphocreatine, glutamate, and lactate) and glial reactivity (e.g., choline and inositol).

<sup>1</sup> Victims of serious assault, people who fall or are struck hard enough to fracture their skull, or people in high-velocity accidents are at increased risk for intracranial abnormalities (14), and these individuals are more likely to be seen in the emergency room. Note that at least 25 percent of people with MTBIs seek no medical attention and 14 percent are seen at their doctor’s office or in clinics (2). Moreover, there is a low risk for observable intracranial abnormalities in athletic concussions, most athletes are not taken to the hospital, and a significant percentage of athletes with minor concussions don’t even report the injury to their coaches or trainers (3). Therefore, the true incidence of structural lesions in *all people* with MTBIs is likely far less than these estimates.

Researchers have reported that some patients with normal CT scans show abnormalities on MRI (29–32) or single photon emission computed tomography (SPECT; 33–35). In some patients with mild or moderate TBIs, brain atrophy can be quantified on serial quantitative MRI over a interval of several months (36, 37). A careful MRI examination of Virchow–Robin spaces (i.e., extensions of the subpial space surrounding perforating arteries and emerging veins serving cerebral cortex—when enlarged, these have been linked to white matter injury) in non-complicated (i.e., 23/24 with GCS of 15 and 20/24 with unremarkable MRI) MTBI might reveal trauma-related findings (38). Abnormalities on positron emission tomography (35, 39) and SPECT (40, 41) have been observed in some patients with persistent postconcussion syndromes. Of course, many patients with chronic complaints do not have abnormalities on functional imaging, such as fMRI (42). Notably, abnormal functional neuroimaging studies do not *diagnose* the presence of an MTBI; there is a large literature on functional imaging abnormalities in patients with diverse neurological or psychiatric problems.

In most people, MTBIs are not associated with macroscopic abnormalities on neuroimaging. Moreover, in animal studies the microscopic damage associated with the milder injuries is very sparse. The physiological changes following MTBI at the cellular level have been examined extensively over the past 20 years, through animal and in vitro modeling. Based on the animal literature, it is assumed that most of the pathophysiology of concussion renders neurons and neural systems *dysfunctional* but *not destroyed*.

Contrary to popular belief, mild (as well as moderate) traumatic brain injury does not result in “shearing” of axons. Axons stretch and twist without being sheared or torn (43–46), even after repeated stretch injuries (47). What was originally conceptualized as “shearing”<sup>2</sup> (48–50) is actually a gradual process where stretched and badly damaged axons swell and eventually separate (43). This process (in MTBI) occurs in a very small number of axons; the vast majority of axons that are initially affected recover over time. The cellular pathophysiology associated with traumatic brain injuries, of all severities, is described in the next section.

### **Pathophysiology**

Advancements in neuroscience have changed our basic understanding of the pathophysiology of neuronal injury. It was once considered that excessive acceleration/deceleration forces caused shear strains on the brain that resulted in tearing or stretching of neurons at the time of

<sup>2</sup>The original neuropathology studies were based on patients with severe TBIs who were rendered in a persistent vegetative state or with severe dementia.

injury (48, 51, 52). Further, it was considered that the brainstem was the focus of injury (53, 54). Taken together, these studies have led numerous clinicians and researchers to conclude that acceleration/deceleration injuries result in shear strains within the cranial vault, and these in turn lead to shearing of neurons and blood vessels occurring principally in the brainstem. Although no one doubts the existence of shearing strains as the primary pathophysiologic mechanism responsible for damage to axons, the pathophysiologic sequence that leads to traumatic injury to neurons is “a process, not an event” (Ref. 55, p. 163).

The Ommaya and Gennarelli (56) model of TBI suggested that acceleration/deceleration forces can cause mechanical strains that occur in a “centripetal sequence.” Injuries of this nature occur when the head is propelled through space and is abruptly stopped by a solid object, such as the ground, or when the head is set into motion, such as when a car is struck from behind by another car. With mild forces, the sequence begins at the surface of the brain and then progressively affects deeper structures as forces become more severe.

Based on their original classification system, the authors postulated three critical predictions. First, when the degree of trauma is sufficient to produce LOC, cortex and subcortical white matter will be primarily affected, with damage to cortex and its associated white matter being more severe than that found in the rostral brainstem. Second, damage to the rostral brainstem will not occur without more severe damage occurring in the cortex and subcortical structures, because the mesencephalon is the last area to be affected by such centripetal forces. Third, cognitive symptoms such as confusion and disturbance of memory can occur without LOC; however, the reverse cannot occur (i.e., LOC cannot occur without accompanying cognitive symptoms) (56). In addition to these critical predictions, the theory reinforced three important aspects of how TBI can occur and the potential effects that different acceleration/deceleration forces have on the brain. First, it reinforced the principle that the *direction* of force can determine severity of injury. Second, a continuum of injury exists whereby mild, moderate, and severe brain injuries caused by acceleration/deceleration forces are not discrete entities but occur on a continuum. This continuum occurs from the surface of the brain inward with increasing amounts of damage occurring at each level of depth as forces increase (49, 57). Third, acceleration/deceleration forces alone are sufficient to cause severe TBI, as supported by research in human trauma cases (58–61). Understanding the importance of acceleration/deceleration forces and their role in the pathophysiology of MTBI can be seen in the number of methods that are being developed to measure these forces in motor vehicles (62) and in athletes (63–66).

It is important to link the presence of acceleration/deceleration forces with the primary mechanism of

injury in the neuron-axonal (and potentially dendritic) stretching. Recent studies have shown that axons of cultured human neurons have a remarkable capacity for stretch with no primary axotomy observed with strains below 65 percent of the length of the axon. In addition, axons exhibit the behavior of “delayed elasticity.” In other words, stretch causes a temporary deformation of an axon that gradually returns to the original orientation and morphology even though internal damage was sustained (67). Once stretched, a pathophysiologic process begins that can lead to further structural change and metabolic dysfunction. First, strain on the axonal membrane causes an abnormal influx of  $\text{Na}^+$  through mechanosensitive sodium channels, a reversal of the  $\text{Na}^+$ - $\text{Ca}^{2+}$  exchangers, and activation of voltage-gated  $\text{Ca}^{2+}$  channels (68). This in turn causes selective proteolysis or a breakdown of  $\text{Na}^+$  channels and progressively increasing levels of intra-axonal  $\text{Ca}^{2+}$  (69). The massive influx of  $\text{Ca}^{2+}$  leads to damage to the axonal cytoskeleton and initiates the pathophysiological process that follows.

Stretching of axons has functional and structural implications. In an animal model, stretch below four millimetres (mm) did not cause any morphological change in axons, a stretch of five mm produced changes in visual evoked potentials that were significantly different from controls, with a six mm stretch causing morphological change including retraction balls and axonal swellings (70). Therefore, a single acceleration/deceleration event might result in (a) no apparent change in structure or function, (b) functional or metabolic change, or (c) eventual structural change in the axon. These outcomes are dependent on the force applied to the brain.

Metabolic dysfunction that occurs in neurons following their exposure to acceleration/deceleration forces and blunt trauma has been recently reviewed (7, 71). Both reviews focus on compromised metabolic pathways that affect cellular energy production systems. Following axonal stretch, small ion species enter the axons at or near the nodes of Ranvier. This initiates metabolic dysfunction and when acceleration/deceleration forces are sufficiently high, will cause damage to the cytoskeleton and microtubules (this process will be described next) (43–46, 72–74). Immediately following this event, there is an indiscriminate release of neurotransmitters and uncontrolled ionic fluxes. The first of these are potassium ( $\text{K}^+$ ) efflux and sustained calcium ( $\text{Ca}^{2+}$ ) influx that activate pumps to restore cellular homeostasis. This will of course affect glucose utilization leading to dramatic increases in the local cerebral metabolic rates. Where this becomes problematic is when “hypermetabolism” occurs in the presence of decreased cerebral blood flow that can impact the functioning of ion pumps. In addition to increased glucose utilization, there may be impaired oxidative metabolism and diminished mitochondrial function. This can lead to the over-reliance on less efficient anaerobic

metabolic pathways. The net effect can be elevated lactate and reduced intracellular magnesium levels (magnesium is a very important component for generation of adenosine-triphosphate [ATP-energy production], the initiation of protein synthesis, and the maintenance of the cellular membrane potential). Mitochondrial accumulations of  $\text{Ca}^{2+}$  can lead to metabolic dysfunction and eventually energy failure (7, 71).

Recently, animal experimentation has provided evidence that depressed mitochondrial functioning might be improved by treatment with hyperbaric oxygenation (75). (See Chapter 57 by McElligott and colleagues in this book for a discussion of this topic.) In humans, magnetic resonance spectroscopy has been useful in detecting additional metabolic changes that can occur following MTBI. N-acetylaspartate (NAA), a marker of neuronal axonal viability, total choline (Cho), a marker of membrane metabolism, total creatine (Cr), which reflects energy status, and lactate (Lac), an indicator of ischemia, were measured at 2–30 days following injury in 14 subjects with an average GCS score of 14.4 (range 13–15) and 10 of 14 with positive CT or MRI indicators of neurotrauma. Significant differences were found for the NAA/Cr ratio in parietal white matter, Cho/Cr ratio in occipital grey matter, and the NAA/Cho in four occipital lobe regions. All three ratios were different in temporal lobe compared to control. The ratios were consistent with decreased NAA and increased Cho found in severe TBI (26).

The sustained influx of  $\text{Ca}^{2+}$  has another important effect; the initiation of a pathophysiologic process of axonal injury. Axons contain numerous microscopic elements including microtubules and neurofilaments. Microtubules are thick cytoskeletal fibers and consist of long polar polymers constructed of protofilaments packed in a long tubular array. They are oriented longitudinally in relation to the axon and are associated with fast axonal transport (76). Neurofilaments are essentially the “bones” or cytoskeleton of the axon and are the most abundant intracellular structural element in axons (76). When acceleration/deceleration forces are sufficient, a massive influx of  $\text{Ca}^{2+}$  leads to damage to the axonal cytoskeleton and initiates the formation of axonal swellings. This process has been reviewed in detail by Gaetz (77) and will be summarized here.

The pathophysiologic events that lead to secondary axotomy associated with animal models of traumatic axonal injury (TAI)<sup>3</sup> occur within minutes of injury. Five minutes after a moderate injury, neurofilament networks appear dense or more tightly packed, and local mitochondrial abnormalities have been observed without any

<sup>3</sup>The term traumatic axonal injury has replaced diffuse axonal injury because the damage is to axons that tend to group in various areas of the brain and are therefore not considered truly “diffuse”.

overt disruption of the overlying axolemma (74, 78). Within 30 minutes of a traumatic injury, scattered axons showed slight swelling, multiple swellings, and/or infolding of the axolemma. When this occurs, there can be focal neurofilament disarray and misalignment of the axon with local axolemmal infolding (74).

In the hours following injury, a gradual progression of axonal pathology occurs in the absence of local hemorrhage or damage in the surrounding tissue. Axonal swelling continues and focal aggregations of organelles occur (including mitochondria and neurotubules) with no physical tearing or shearing of the axon cylinder (43). Over a period of hours, this process leads to some axons having focal swellings with others in early stages of disconnection due to a disruption of axoplasmic transport (45). At three hr post-injury a further axonal change is observed including disconnection of the axon with continued expansion to form a mature reactive swelling. Some reactive axons display a proximal stump undergoing continued swelling due to increased accumulation of organelles capping an expanding neurofilamentous core (74). At four to six hr following brain injury, proximal and distal swellings are further enlarged, more complex, and are often separated by a thin strand of protein linking the two segments (43).<sup>4</sup> At 12–24 hr post-injury, Povlishock et al. (43) reported that swellings had progressed to resemble enlarged ball-like expansions with no continuity that could be identified between their proximal and distal axonal segments, suggesting an abrupt separation of the axon cylinder.

From 24 to 72 hr in animals, a further enlargement of cleanly separated axons was observed, with some showing what was assumed to be a regenerative attempt in the form of growth cones that protruded from reactive axonal swellings (45). At 24 hr in humans, the reactive swellings exhibit further change in their appearance and the process of axonal separation begins. From 30 hr to one week, grossly swollen axonal segments disconnected from one another are observable in humans (46, 73). At three to four days following injury, Povlishock and Becker (44) noted that the injury profiles differed from axon to axon. By 88 hr in humans, further progression of the reactive swellings had occurred with heterogeneity observed among the population of reactive axons (46).

At 5–7 days, various forms of reactive change were identified (44). This pattern continues until 9–14 days

<sup>4</sup>This pathophysiologic process has been observed in humans following fatal motor vehicle accidents and *severe* brain injury (46, 73), although it appears to occur more slowly in humans. The degree to which this pathophysiological process occurs following MTBI, and the numbers and locations of cells involved, is unknown. Nonetheless, it very likely occurs in patients with MTBIs of the more serious nature, such as complicated MTBIs or MTBIs resulting from high speed motor vehicle accidents.

two conditions are predominant (44). In one group of cells, the degenerative response continued, displaying several retrogressive changes such as lobulation, increased electron density, and axolemmal/axoplasmic disruption, all of which were accompanied by focal macrophage accumulation. In another group of cells, a regenerative response was observed (44). At 17–30 days, regenerative or degenerative axonal changes predominated. Macrophages observed in the presence of degenerating axons actively phagocytosed the damaged swellings. Some of these pathophysiologic changes were observed by Oppenheimer (79) decades ago. Recently, Bigler (80) reported single case autopsy data showing “scattered macrophages in the white matter” in the frontal and temporal lobes in a patient with an MTBI who died from other causes several months post injury. This patient was in a high speed MVA, his vehicle was “demolished,” he suffered cervical fractures due to projectiles, he had an initial GCS of 14, LOC of unknown duration, no significant post-traumatic amnesia, and a head CT that did not appear to show a trauma-related abnormality.

The changes observed in animal models and humans are consistent with a progressive series of neurophysiologic events initiated by acceleration/deceleration forces on the axon, and ending in some cases with a frank separation of proximal and distal axon segments. As Povlishock and Becker (44) stated, it had been long assumed that axonal shear or tensile force caused a physical disruption of the axon into a proximal and distal segment. These studies provide evidence contrary to the shearing hypothesis, and instead, suggest that even relatively low-intensity mechanical brain injury produces axonal change that is more subtle than that suggested previously (i.e., direct tearing of the axon).

Neuroscience has not only provided a new vantage point to consider the pathophysiology of injury, it has given us a better understanding about which neurons are vulnerable to injury. Early studies suggested that the brainstem was the primary site of injury (e.g., Refs 81, 82). However, recent studies point to cellular injury that does not specifically involve the brainstem, especially with injuries produced by mild to moderate forces. Various characteristics of neurons themselves appear to make them more susceptible to injury: when axons change direction, enter target nuclei, or when they decussate, they can be more easily damaged (45, 73, 79, 83, 84). Large caliber neurons are injured more often than smaller neurons that surround them (45). Of particular importance, injured axons are observed more often where a change in tissue density occurs, such as at the grey/white matter interface near cerebral cortex (49, 73, 84, 85), a finding supported by functional neurophysiology (86) and MRI. Because the cerebral cortex plays a substantial role in maintaining a distributed consciousness (87), trauma involving cortex and sub-cortical white matter will affect

consciousness because brainstem reticular cells will be suppressed due to a lack of input.

The features of cellular injury, dysfunction, and death have been described in detail in this section. It is important to appreciate that cell death is closely related to injury severity. Mild traumatic brain injuries, especially injuries on the milder end of the spectrum, are typically characterized by cellular dysfunction that is reversible. There is a continuum of injury, at the cellular level, ranging from completely and rapidly reversible cellular dysfunction, to slow but complete recovery, to slow and incomplete recovery, to cell death. Very mild concussions likely produce virtually no permanent damage to cells resulting in long-term symptoms or problems whereas severe traumatic brain injuries, especially those involving considerable forces, often produce widespread cellular death and dysfunction with clear functional consequences; complicated MTBIs and moderate TBIs likely fall in between.

### **S-100B AS A MARKER OF INJURY AND A PREDICTOR OF OUTCOME**

Over the past decade, there has been an increased interest in the role of various biochemical markers for use as diagnostic and prognostic measures of brain damage in the first few days post-TBI (88, 89). Biochemical markers are of great interest because they may provide a more cost effective and efficient measurement of brain damage than can be assessed in the acute treatment phase. Clinicians typically rely on static imaging techniques such as CT and MRI to determine the extent of brain damage. However, CT scanning tends to have a low sensitivity to diffuse brain damage and the availability of MRI is limited in many settings due to high costs (89). There is a growing body of research literature suggesting that the neuroprotein S-100B may be a reliable marker for brain damage (e.g., 88–95). S-100B is a calcium binding protein which is found in high concentrations in astroglial and Schwann cells, predominantly in the central nervous system. When these cells are structurally or ischemically damaged, it is believed that S-100B is rapidly released into the cerebrospinal fluid (CSF) and secondarily across the blood-CSF barrier into circulation (91). Measurements of S-100B are acquired from serum obtained from a standard blood sample (90). If the neuroprotein S-100B could be established as a reliable marker of brain damage, S-100B has the potential to serve as a cost-effective measure to (a) initially screen patients in the first hr post injury to detect brain damage, (b) monitor the occurrence of secondary complications during recovery, and (c) be used to predict future outcome (96).

Researchers have reported that the concentration level of S-100B is significantly higher in patients with MTBIs than in controls (91, 94, 97, 98). Unlike Glasgow

Coma Scale (GCS) scores, the presence of alcohol at the time of injury does not influence the serum concentrations of S-100B in patients with MTBIs or healthy controls (92, 98), even in injured patients with blood alcohol levels of 2.5 to 5 times (i.e., 250–500 mg/dl) the legal level of intoxication (91).

Researchers have reported that S-100B levels are associated with (a) the presence of brain abnormalities detected by CT scans (91, 95, 98, 99), (b) prediction of severe outcome 1 month post-injury as measured by the Extended Glasgow Outcome Scale (100), (c) the rate of failure to return to work 1 week post-injury in patients with very mild brain injuries (101), (d) injury severity as measured by the GCS and the Coma Remission scale (95, 97, 99, 102, 103), and (e) the presence of neuropsychological deficits 2 weeks and 6 months post-injury (95). However, not all studies have been as favorable. Some researchers have reported that S-100B levels taken directly after injury are *not* associated neuropsychological test results at 7 to 21 days post injury in an uncomplicated mild TBI sample (104) or with PCS symptom reporting 1-year following MTBI (105).

Although much of the research in this area does support a relationship between S-100B levels and outcome following MTBI, there are a number of limitations of using S-100B as a diagnostic marker for brain damage in this population. S-100B tends to be a sensitive marker for brain damage, but not a very specific marker. Various studies have examined the clinical value of S-100B levels to predict various outcomes from TBI such as abnormal CT scans (91, 97, 99, 103), abnormal MRI scans (106), severe disability as measured by the Extended Glasgow Outcome Scale scores (100), and return to work rates (101). A summary of the sensitivity, specificity, and predictive power values for S-100B to predict these outcomes is presented in Table 22-5. The results from these studies are remarkably consistent. Across all studies, sensitivity is high to very high (range = 80–100 percent) and specificity is moderate to high (range = 40.5–81 percent). However, positive predictive power (PPP) values are low to moderate (range = 21–40.5 percent). In contrast, negative predictive power (NPP) is very high (range = 95.1–100 percent).<sup>5</sup> Ideally, it is preferred for all four measures to be high. However, in these studies, only sensitivity and NPP have acceptable values. Nonetheless, these studies can provide some important information for prediction of outcome from MTBI using S-100B. These studies suggest that although S-100B *is not useful* for identifying individuals who are “at risk” of poor outcome from TBI (i.e., PPP), it *is useful* for identifying those individuals who are “*not* at risk” of poor outcome from TBI (i.e., NPP; individuals who will have a good outcome

post-injury). As a diagnostic tool, the practical implication of this finding is that S-100B measures will misidentify a significant portion of individuals “not at risk” (i.e., good outcome) as being “at risk” (i.e., poor outcome). That is, the test will be positive and they will falsely be labelled as being at risk for poor outcome. Theoretically, this could lead to unnecessary treatment or unnecessary worry for the patient. To our knowledge, there is no research that has compared the diagnostic accuracy of S-100B to current clinical decision rules.

Another limitation is the extracranial release of S-100B (105). Elevated S-100B levels have been found in trauma patients who *have not* sustained a head injury (107) and in healthy subjects involved in various sports (108–110). Anderson and colleagues found that S-100B levels measured immediately after admission to the emergency department were most elevated in trauma control subjects who had incurred bone fractures. However, patients with soft-tissue injuries and burns also had elevated S-100B levels that were 40 times greater than healthy controls<sup>6</sup> (107). Researchers examining athletes have found that the release of S-100B increases after various sporting activities compared to pre-activity levels (108–110). However, participation in certain sports results in the release of S-100B levels differently. Otto and colleagues found that competitive boxing resulted in the highest increase of S-100B, followed by jogging, running, 25km race, and sparring (108). Stalnacke and colleagues also found similar increases in S-100B levels in elite basketball, ice hockey, and soccer players (109, 110). Otto and colleagues hypothesised that the increase in S-100B after running activities may be the result from “brain tissue, axial vibration of the brain at each step” during the jogging and running action (108). This hypothesis, however, is purely speculative at this time. Although these studies do show that participation in various sports increases S-100B levels, the increase is lower than in patients who have sustained an MTBI (108, 111).

Methodological differences between studies make drawing any conclusions regarding the efficacy of S-100B as a useful marker for brain injury difficult. One major methodological difference relates to the time post-injury S-100B is measured. Measurement of S-100B greatly varies across studies ranging from as quickly as 44 minutes post-injury (93) to as long as 27 hr post-injury (95, 102). The majority of studies have measured S-100B within either 2 hr (97, 98, 100), 4 hr (99, 101, 103, 105), or 6 hr post-injury (94, 104, 112). This is an important issue because it is thought that S-100B levels rapidly increase in the circulation system within the first few minutes of injury, reaching a concentration peak within 20 min (91). S-100B is then eliminated quickly by renal

<sup>5</sup> See the table note in Table 22-5 for an explanation of these statistics.

<sup>6</sup>This study highlights the importance of comparing trauma controls to TBI in research studies.

**TABLE 22-5**  
*Summary of Sensitivity, Specificity and Predictive Power Values of S-100B Levels to Predict Outcome*

FIRST AUTHOR	N	COUNTRY	SETTING	SAMPLE TYPE	TIME OF BLOOD SAMPLE	S-100B CRITERIA	OUTCOME	SEN.	SPEC.	PPP	NPP
Stranjalis 2004	93	Greece	Hospital ED	MTBI (GCS = 15)	3 hr	0.15 µg/L	Failure to return to work 1 week post-injury (Yes/No)	80	74.4	37.5	95.1
Mussack 2002	20	Germany	Level 1 Trauma	Severe TBI (GCS 3–8)	M = 43.8 min (range 22.6–72.4 min)	0.76 ng/mL	“Unfavorable outcome” defined by GOS = 1–3	100	50	24.1	100
Biberthaler 2001	52	Germany	Level 1 Trauma	MTBI (GCS 13–15)	116 mins (SD = 18.8 mins)	0.1 ng/mL	Abnormal CT scan	100	40.5	40.5	100
Townend 2002	148	England	Hospital ED x 4	Mild-Severe TBI (88 percent GCS = 15)	M = 130 mins	0.32 µg/L	Severe disability at 1 month post-injury: GOSE < 5	93	72	33	99
Ingebrigtsen 2000	182	Norway Sweden Denmark	Hospital ED	MTBI (GCS = 13–15)	Within 3 hr	0.2 µg/L	Abnormal CT scan	90	65	13	99
Ingebrigtsen 1999	48	Norway Sweden Denmark	Hospital ED	MTBI	Within 6 hr	0.2 µg/L	Abnormal MRI scan	80	81	33	97
Romner 2000	278	Norway Sweden Denmark	Hospital ED	Mild-Severe TBI (91 percent MTBI)	M = 3.8 hr (range = 0.5 to 24 hr)	0.2 µg/L	Abnormal CT scan	92	66	21	99

*Note:* GOSE = Extended Glasgow Outcome Scale; GOS = Glasgow Outcome Scale; Sen = Sensitivity; Spec = Specificity; PPP = Positive predictive power; NPP = Negative predictive power.

For these studies, sensitivity, specificity, and predictive power statistics evaluate the ability of S-100B levels to predict, for example, abnormal CT and MRI scans, severe disability as measured by the GOSE, and return to work rates. Sensitivity is the true positive rate for a test/measure. It answers the question: knowing that the individual has a positive CT scan (for example), what percentage of these individuals will actually be correctly identified as having a positive CT scan using S-100B. Specificity is the true negative rate for a test/measure. It answers the question: knowing that that individual has a negative CT scan, what percentage of these individuals will actually be correctly identified as having a negative CT scan using S-100B. However, positive predictive power (PPP) and negative predictive power (NPP) are the statistics most suited as a diagnostic tool in a clinical setting (n = 1). These statistics provide us with information relating to how confident we can be, in terms of a percentage, that a given score on a test/measure actually predicts what the test is designed to predict. PPP statistics answer the question: knowing that the person has been classified as likely to have a positive CT scans based on S-100B, what is the probability that the person will actually have a positive CT scan. On the other hand, NPP statistics answers the question: knowing that the person has been identified as likely to have a negative CT scan using S-100B, what is the probability that the person will actually have a negative CT when scanned.

*Sources:* Stranjalis 2004 (101); Mussack 2002 (91); Biberthaler 2001 (97); Townend 2002 (100); Ingebrigtsen 2000 (103); Ingebrigtsen 1999\* (106).

\*Data extracted from Ingebrigtsen and Romner (88).

metabolism and urinary excretion (113), with a number of studies demonstrating a significant decline in S-100B within the first few hours after injury (e.g., 95, 99, 102, 105). S-100B is estimated to have a biological half-life ranging from 30 to 113 min (91, 113, 114). To date, there is no consensus in the literature on the dynamics of S-100B after TBI (104) or when is the right time to measure it (105). There is a lack of knowledge regarding how quickly S-100B is released following injury and how quickly it is eliminated by the body (104). While current research shows promise for S-100B as a marker for brain damage, much more research will be required before this biochemical marker will be accepted as a reliable measure of brain injury. Future research must strive to understand the dynamics (i.e., time of release and elimination) of S-100B after TBI and employ trauma control subjects to determine whether S-100B levels are unique to TBI.

### NEUROPSYCHOLOGICAL OUTCOME

Historically, some researchers and clinicians believed that loss of consciousness (LOC) was necessary for the *diagnosis* of MTBI. In the 1920s, Symonds (115) discussed the importance of traumatic LOC as an essential feature of concussion. He said that in

the initial stage the patient is completely unconscious and in a state of flaccid paralysis. In a severe case the respiratory and cardiac functions may hardly continue. In a few minutes recovery begins; the visceral reflexes are the first to return, and vomiting is common at this stage. The other cerebral functions recover more gradually, and there may be a phase of some hr during which consciousness is clouded. Following this again there may be complaint of headache and giddiness, but at the end of twenty-four hr in an uncomplicated case of concussion recovery should be complete.” (p. 829)

Of course, it has been recognized for many years that concussions can occur without LOC (e.g., 116). In fact, the vast majority of injuries in sports (117–119) and many injuries in medical trauma settings (e.g., 120–122) are not associated with LOC. The presence or duration of LOC is not always used as a criterion for MTBI in research studies (see Ref. 10 for a review).

The more interesting question is whether brief loss of consciousness is associated with worse outcome. Gennarelli and colleagues conducted an extraordinary series of primate studies (e.g., 123) illustrating that both the presence of diffuse axonal injury (i.e., traumatic axonal injury) and functional outcome are associated with duration of unconsciousness (i.e., coma). It is certainly well known that an *extended* period of unconsciousness/coma in humans is associated with poor long-term outcome. Repeated demonstrations in the literature of worse outcome

associated with more severe brain injuries—as defined by duration of coma—can understandably influence scientific beliefs regarding the importance of traumatic LOC in *very mild* injuries, such as those sustained in sports. There is no doubt, as a general rule, that patients with comas lasting 1–2 weeks have worse outcome than patients with comas lasting less than 24 hr (e.g., 124). However, this logic should not be assumed to hold true for MTBI. Researchers studying trauma patients have reported that there is no association between *brief* loss of consciousness and short-term neuropsychological outcome (e.g., 121, 125, 126) or vocational outcome (120). Some researchers examining *athletes* with concussions have reported an association between LOC and immediate or short-term outcome (e.g., 127–129), while others have not (e.g., 130, 131). However, athletes with concussions, as a rule, recover relatively quickly and fully (see the chapter by Collins, Iverson, Gaetz, and Lovell in this book for a review). Therefore, based on the literature to date, it would be a mistake to assume that brief LOC is a reliable predictor of worse short-, medium-, or long-term outcome in trauma patients.

### Post-Traumatic Confusion and Amnesia

Post-traumatic amnesia (PTA) has been related to outcome in many (e.g., 132–136) but not all (e.g., 137) studies involving patients with moderate to severe traumatic brain injuries. By inference, mainly, it is often presumed that PTA is also a predictor of outcome following mild traumatic brain injury. However, the duration of PTA in mild cases is difficult to determine because, by definition, it is a relatively short period of time and it is rarely assessed prospectively. The accuracy of retrospective reports of PTA is questionable.

Post-traumatic amnesia lasting more than 30 min in patients with MTBIs has been associated with cerebral hypoperfusion on day-of-injury SPECT scans (33). The presence and duration of post-traumatic confusion/amnesia has been associated with worse immediate outcome and slower recovery in athletes (128–130, 138, 139). Again, the literature regarding athletes is less relevant because they tend to recover quickly.<sup>7</sup> For trauma patients, there appears to be a relation between post-traumatic confusion/amnesia and short-term neuropsychological outcome (see the original data presented in Tables 22-7 and 22-8), but by three months post-injury this association may disappear (140). Some researchers have reported that duration of post-traumatic amnesia is related to one-year return to work rates, but this effect

<sup>7</sup>Athletes tend to be young, very healthy, highly motivated, and they usually don't have co-morbid conditions that might slow down recovery from MTBI or mimic the postconcussion syndrome in the post-acute period.

**TABLE 22-6**  
*Demographic and Injury Severity Variables by Post-Injury Confusion Groups*

VARIABLE	GOAT > 89 (N = 527)	GOAT < 90 (N = 227)
Age	26.0 (6.9)	26.1 (6.4)
Education	12.1 (1.8)	11.8 (2.0)
Gender	Male = 69.3 percent	Male = 72.7 percent
Race	Caucasian = 94.7 percent African-American = 3.3 percent Hispanic = 1.9 percent	Caucasian = 93.4 percent African-American = 5.5 percent Hispanic = 1.1 percent
Skull Fracture	18.0 percent	18.5 percent
Abnormal CT	12.5 percent	16.9 percent
GCS = 15	89.9 percent	73.6 percent
GCS = 14	10.1 percent	26.4 percent
Positive LOC	60.4 percent	65.7 percent
Negative or Equivocal LOC	39.6 percent	34.3 percent

GOAT = Galveston Orientation and Amnesia Test; GCS = Glasgow Coma Scale

**TABLE 22-7**  
*Neuropsychological Test Results for Persons With Versus Without Evidence of Post-Injury Confusion or Amnesia and Negative CT-Scans*

VARIABLE	GOAT > 89 (N = 175)		GOAT < 90 (N = 157)		P	EFFECT SIZE
	M	SD	M	SD		
Trails A	28.3	9.3	31.0	12.0	<.026	.25
Trails B	69.1	25.8	84.6	43.9	<.001	.43
COWAT	37.1	9.0	35.1	10.3	<.070	.21
WCST-64 Categories	3.6	1.4	3.4	1.5	<.422	.09
WCST-64 Perseverative Responses	9.9	7.3	10.0	7.4	<.929	.01
HVLT Total	24.3	3.9	22.1	4.7	<.001	.52
HVLT Delay	8.3	2.4	7.0	2.9	<.001	.47
Logical Memory I	23.6	6.3	21.8	6.7	<.024	.27
Logical Memory II	19.2	7.3	16.5	8.0	<.004	.36
Visual Reproduction I	33.5	4.9	32.0	5.9	<.018	.28
Visual Reproduction II	30.4	6.6	26.9	9.0	<.001	.44
Logical Memory Savings	80.4	20.1	72.2	24.4	<.004	1.12
Visual Reproduction Savings	90.3	14.6	82.4	22.0	<.001	.42
Digits Forward	8.8	1.8	7.8	2.0	<.001	.54
Digits Backward	6.5	2.2	5.8	2.3	<.006	.32

COWAT = Controlled Oral Word Association Test; WCST-64 = Wisconsin Card Sorting Test - 64; HVLT = Hopkins Verbal Learning Test. Effect Sizes (Cohen's d): small = .2, medium = .5, and large = .8.

was mostly due to the inclusion of patients with moderate TBIs and PTA greater than 24 hr (141).

### Complicated MTBIs

Commonsense would suggest that patients with complicated MTBIs (i.e., bleeding, bruising, or swelling on their

day-of-injury CT) would have worse short-, medium-, and long-term outcome than patients without obvious structural damage. Surprisingly, the literature is somewhat mixed on this issue. In most studies, patients with complicated MTBIs perform more poorly on neuropsychological tests in the initial days and weeks post injury (142–144), and they appear to have worse 6–12 month



**TABLE 22-8**  
**Neuropsychological Test Results for Patients with Abnormal CT-Scans**

VARIABLE	GOAT > 89 (N = 25)		GOAT < 90 (N = 32)		P	EFFECT SIZE
	M	SD	M	SD		
Trails A	33.6	15.4	32.6	9.4	<.765	.08
Trails B	88.8	37.0	95.8	41.3	<.523	.18
COWAT	27.9	9.0	31.1	10.7	<.239	.33
WCST-64 Categories	3.5	1.3	2.8	1.7	<.064	.53
WCST-64 Perseverative Responses	11.6	8.5	16.7	17.1	<.169	.38
HVLT Total	22.3	4.5	20.2	4.5	<.167	.46
HVLT Delay	7.6	2.6	4.5	2.7	<.002	1.15
Logical Memory I	22.7	7.3	21.4	7.2	<.542	.18
Logical Memory II	17.0	8.1	11.6	8.4	<.028	.65
Visual Reproduction I	33.7	5.2	29.2	7.1	<.015	.71
Visual Reproduction II	30.9	5.1	21.5	9.6	<.001	1.23
Logical Memory Savings	70.4	26.0	51.8	30.8	<.030	.65
Visual Reproduction Savings	92.3	11.9	71.6	24.0	<.001	1.09
Digits Forward	7.9	1.9	7.9	2.1	<.972	.01
Digits Backward	5.7	2.0	5.8	1.8	<.845	.05

COWAT = Controlled Oral Word Association Test; WCST-64 = Wisconsin Card Sorting Test - 64; HVLT = Hopkins Verbal Learning Test. Effect Sizes (Cohen's d): small = .2, medium = .5, and large = .8.

(11, 30, 145) and 3–5 year (146) outcomes than patients with uncomplicated MTBIs. In contrast, some researchers have reported no differences (120) or equivocal differences associated with early structural abnormalities (36, 147). In a well-controlled prospective study, McCauley and colleagues reported that CT abnormalities were not associated with increased risk for postconcussion syndrome at 3 months post injury (148).

### Original Research: Relation Between Post-Traumatic Confusion and Neuropsychological Outcome

There has been very little research that has examined the relation between post-traumatic amnesia and short-term neuropsychological outcome in trauma patients. We present here original data in a carefully defined sample of young adult trauma patients with mild traumatic brain injuries who completed neuropsychological testing within the first week post injury. Participants were selected from a large database ( $N = 1,695$ ) of patients seen on the Trauma Service of Allegheny General Hospital in Pittsburgh, Pennsylvania between May of 1991 and June of 1994. The basic clinical pathway for any person with known or suspected brain injury, irrespective of severity, involved a GCS rating, skull x-ray, CT scan of the brain, and an assessment of post-traumatic amnesia with the Galveston Orientation and Amnesia Test (GOAT; 149).

To be included in this study, patients must have (a) had a GCS score of 14 or 15, (b) been under 40 years of age, and (c) been tested within *seven days post injury*. The total sample consisted of 484 patients who met these criteria. The average age of the total sample was 26.0 (SD = 6.7) years and their average education was 11.9 (SD = 1.9) years. Seventy-one percent were male and 29 percent were female. The mechanisms of injury for the patients were as follows: (i) motor vehicle accident without seatbelt = 47.5 percent, (ii) motor vehicle accident with seatbelt = 15.1 percent, (iii) falls = 10.1 percent, (iv) motorcycle with helmet = 7.6 percent, (v) struck by object = 6.2 percent, (vi) pedestrian = 4.3 percent, (vii) other = 4.1 percent, (viii) missing = 3.5 percent, and (ix) motorcycle with no helmet = 1.5 percent. Eighteen percent had GCS scores of 14 and 82 percent had scores of 15. The breakdown regarding loss of consciousness for the sample was 55.6 percent positive, 17.8 percent negative, 15.1 percent equivocal, and 11.6 percent missing. Skull fractures were present in 16.1 percent, absent in 72.3 percent, and missing in 11.6 percent of cases. The prevalence of intracranial abnormalities on day-of-injury CT was 11.8 percent. The remaining subjects had negative (68.6 percent) or missing (19.6 percent) results. Because 19.6 percent of the sample either did not undergo CT-scanning or their results were not coded into the database, it can be assumed that the actual prevalence of intracranial abnormalities was higher than 11.8 percent.

The patients underwent 35–45 minutes of neuropsychological testing. The tests administered are listed in Tables 22-7 and 22-8. Trails A and B are from the Halstead-Reitan Neuropsychological Battery (150). As tests of information processing speed, they require visual-motor tracking and sequencing. The Trails B test is more difficult because it requires set shifting (i.e., alternating between numbers and letters) during the sequencing task. Digit Span, Logical Memory, and Visual Reproduction were administered from the Wechsler Memory Scale-Revised (151). The ability to repeat a series of digits forward and backward is a measure of attention-concentration and mental control. The Logical Memory (LM) subtest is a memory test for stories. Two stories are read, one at a time, and the subject is asked to recall everything he or she can remember from the story. There is an immediate recall trial (Logical Memory I) and a 30-minute delayed recall trial (Logical Memory II). The LM percent retention score reflects the percentage of information retained after the delay interval (i.e., LMII/LMI). The Visual Reproduction subtest is a memory test for geometric designs. Each design is presented to the subject for 10 seconds, removed, and then the subject is instructed to draw it from memory. After 30 minutes the subject is asked to reproduce all of the previously presented designs (Visual Reproduction II; VRII). The Visual Reproduction retention score is derived by dividing VRII by VRI. The Controlled Oral Word Association Test (152) is a measure of lexical verbal fluency. Patients are given a letter of the alphabet (e.g., C, F, or L) and asked to orally-generate as many words that they can that begin with that letter.

The Wisconsin Card Sorting Test-64 (WCST-64; 153–154) is an abbreviated version on the WCST (155). The WCST contains two decks of 64 cards that the patient must sort on the basis of certain characteristics. This is a nonverbal problem-solving test. The WCST-64 employs only the first of the two decks (156). The Hopkins Verbal Learning Test (HVLT; 157) is a 12-item, three trial word list learning test. The original test has been modified to contain a delayed recall and recognition trial, and normative data are available (158).

The patients were sorted into two groups on the basis of their GOAT scores. Those with GOAT scores of 90 or more were viewed as having no obvious, sustained post-injury confusion. Those patients with scores below 90 were considered to have possible to probable post-injury confusion or amnesia. A score of 90 was the closest value to a median split, with 53 percent of the total sample in the higher group and 47 percent in the lower group. Demographic and injury severity characteristics of the two groups are presented in Table 22-6. The patients with lower GOAT scores had a greater proportion of subjects with GCS scores of 14 ( $X^2(1) = 22.0, p < .001$ ). The groups did not differ in their proportions of patients

with skull fractures ( $p < .90$ ), CT abnormalities ( $p < .22$ ), or loss of consciousness ( $p < .27$ ).

Descriptive statistics, mean comparisons, and effect sizes for the neuropsychological tests in the patients with *normal* CT-scans by group are presented in Table 22-7. The groups did not differ in age ( $t(482) = -.16, p < .88$ ) or education ( $t(461) = 1.6, p < .12$ ). The groups did not differ in gender ( $p < .41$ ) or in race ( $p < .49$ ), based on chi square analyses. The patients with high versus low GOAT scores were compared using parametric or non-parametric pairwise tests. Levene's test for equality of variances was used to determine whether the t-test was appropriate, or whether a nonparametric test should be used. The Kolmogorov-Smirnov procedure was used to determine whether the variables had non-normal distributions. Although the t-test is rather robust in regards to violations of general linear model assumptions (e.g., normally distributed variables and homogeneity of variance), nonparametric analyses (i.e., Mann-Whitney U tests) were conducted on most variables because heterogeneity of variance or non-normal distributions were present. The probability of Type 1 error increases when multiple statistical comparisons are conducted, so the reader should have the most confidence in findings that are below  $p = .01$ . Using this criterion, the patients with lower GOAT scores also scored significantly worse on Trails B, HVLT total and delayed recall scores, Logical Memory II and savings scores, Visual Reproduction II, and Digit Span Forward and Backward.

Descriptive statistics, mean comparisons, and effect sizes for the neuropsychological tests in the patients with *abnormal* CT-scans are presented in Table 22-8. The groups did not differ in age ( $t(55) = -.8, p < .43$ ) or education ( $t(52) = .5, p < .61$ ). The patients with high versus low GOAT scores were compared with parametric (i.e., independent *t*-tests) and nonparametric (i.e., Mann-Whitney U) tests using the same procedures as reported for the patients with normal CT-scans. Although there were fewer significant findings, there was still a clear pattern of worse neuropsychological test performance in persons with lower GOAT scores. It should be noted that the significance values in Table 22-8, as compared to Table 22-7, are reduced as a function of sample size. By examining estimated effect sizes, it can be seen that variables with medium to large effect sizes, if stable, would be "more significant" if the sample sizes were increased.

In the present investigation, patients were sorted on the basis of their GOAT scores into high and low groups through an approximate median split. This is not a conventional method for examining GOAT scores. Rather, it is an attempt to estimate more subtle aspects of post-injury confusion as opposed to simply identifying frank PTA (i.e., GOAT scores below 75, which infrequently occur in people with MTBIs). The groups did not differ

in age, education, gender, race, frequency of skull fracture, frequency of abnormal CT scans, or frequency of positive LOC. Not surprisingly, at admission, those with lower GOAT scores had lower GCS scores (i.e., a greater proportion had scores of 14). On the neuropsychological tests, significant differences emerged on several variables measuring aspects of concentration, processing speed, learning, verbal memory, and visual memory. This same methodology, when applied to similar groups but with loss of consciousness (LOC) as the independent variable, failed to reveal any significant differences on the neuropsychological tests (121, 125, 159). Therefore, when trauma patients are evaluated shortly after an MTBI, there is good evidence that post-traumatic confusion is related to worse short-term neuropsychological outcome and good evidence that brief traumatic LOC (e.g., less than 5 min) is *not* related to short-term neuropsychological outcome. Of course, these findings relate to short-term outcome (first few weeks post injury). To best understand long-term outcome, one should consider the results from several recent meta-analytic reviews of the literature.

### Results From Meta-Analyses

A large number of prospective studies and several recent meta-analyses have greatly enhanced our understanding of the natural history of MTBI. Trauma patients and athletes often report extensive symptoms, and they perform more poorly on neuropsychological tests, in the initial days (118, 119, 128, 147, 160, 161) and up to the first month following the injury (e.g., 118, 140, 162, 163, 164). Due to natural recovery, neuropsychological decrements typically are not seen in athletes after 2–21 days (3, 118, 119, 160, 161, 165), and in trauma patients after 1–3 months (e.g., 140, 166, 167) or certainly a year (e.g., 124, 168–171) in prospective group studies. Several meta-analyses (4, 6, 8, 172) and recent reviews (5, 7, 173) of this literature are available and, as a rule, report very good neuropsychological outcome from MTBI.

Clinicians and researchers should carefully, deliberately, and critically read the literature relating to MTBI in trauma. Historically, the majority of studies over the decades have not been carefully controlled or prospective. It is essential to study the selection criteria and methods to appreciate the characteristics of the sample and the population to which that sample might generalize. Over the decades, there have been varying degrees of prevailing beliefs and themes that MTBIs (a) are minor injuries with no long-term consequences, (b) are serious injuries that frequently result in significant long-term consequences, or (c) are significant injuries that result in short-term consequences for most people and medium-term consequences for some. A person holding any particular belief or bias regarding MTBI can easily support that

view using select studies within the existing literature. It is getting increasingly difficult, however, to find good scientific evidence that MTBIs are associated with demonstrable cognitive deficits or symptoms that are due to the biological effects of the injury in more than a small minority<sup>8</sup> of patients who are more than 3 months post-injury.

Neuropsychological meta-analyses allow us to quantify the effects of certain injuries, conditions, or diseases on cognitive functioning. These aggregated estimates of effect size are important because they consider the literature as a whole and typically are based on hundreds, if not thousands, of subjects. The fact that clinical groups overlap substantially with the normal population, and with each other, is poorly understood amongst clinicians and researchers. Researchers, reporting the results from individual studies, emphasize the differences between groups that are statistically significant, and then write that group A could be “differentiated” from group B on the basis of these statistically significant findings. Small differences between groups can be statistically significant, but what is typically not reported is that the two groups are far more similar than they are dissimilar. Clearly, small statistically significant differences between groups might not have any practical, clinical, or real-world significance.

The distributions of neuropsychological test performance across diagnoses, circumstances, or conditions, based on meta-analytic reviews of the literature, are illustrated in Figure 22-1. The shaded line in the middle represents the average score for healthy normal adults (i.e., a z-score of zero). The upper and lower shaded lines represent the expected scores for 50 percent of healthy adults. Similarly, 80 percent of healthy adults are expected to score between the solid lines. As seen in the second column, 90 percent of normal adults are expected to score between the upper and lower “90.” The ranges of scores for all of the clinical groups are based on the theoretical normal distribution. Deviations from normal (i.e., neuropsychological deficits) are based on the effect sizes reported in the meta-analyses, and for each clinical group one can see the spread of scores expected for 80 percent and 90 percent of that particular group.

In the third column, notice that athletes tested within the first 24 hr post-injury have a marked deviation from normal (effect size of  $-1.0$ ), similar to the deviation seen in patients with moderate to severe traumatic brain injuries who are tested within the first six months post injury (effect size of  $-1.0$ ). This illustrates the major adverse effect of concussion on neuropsychological functioning immediately after injury. However, after seven

<sup>8</sup>This “small minority” cannot be determined at this time but it is likely less than the 15-20 percent estimates in the past literature.

days (column 5), concussed athletes' neuropsychological functioning has essentially returned to normal<sup>9</sup> (as reported in this meta-analysis of the literature). Notice that there are relatively small deviations from normal in patients with MTBIs, and by 1–3 months post injury they cannot be distinguished from the general population. The effects of MTBI on neuropsychological functioning, after the acute recovery period, are considerably less than the effects of litigation, depression, or ADHD. A striking feature of Figure 22-1 is the substantial overlap in expected scores across the clinical groups. In other words, the overall neuropsychological test performances of people in these groups are much more similar than they are dissimilar.

Clearly, our ability to accurately detect cognitive and neurobehavioral decrements associated with an MTBI, through interview, rating scales, or neuropsychological testing, diminishes in tandem with the passage of time. This, of course, is due to recovery. Nonetheless, in clinical practice, we frequently see patients who do not return to their pre-injury level of functioning and who are highly symptomatic. These patients frequently are conceptualized as having poor outcome following an MTBI, and the MTBI is believed to be the direct and/or indirect cause of the poor outcome. These people are typically diagnosed with the controversial persistent postconcussion syndrome.

Differential diagnosis is very important in these cases. The clinician should try to identify and treat the underlying cause, or causes, of these symptoms and problems (which can be diverse, and include cranial and/or cranial adnexal injury, cervical injury, psychological problems and disorders, or pain disorders). Ideally, clinicians should try to *prevent* poor outcome in people who have suffered a MTBI. There is reasonably good evidence that early intervention, as simple as education and reassurance of a likely good outcome, can be effective for reducing symptoms and problems in most patients.

## EARLY INTERVENTION

A number of intervention protocols designed to minimize persisting problems following MTBI have been described in the literature for some time (e.g., 174–176). In the early studies, researchers reported that simple intervention programs applied within the first 3 weeks post-injury can reduce the number and frequency of post-concussion symptoms (177) and increase return to work rates (178).

The content of early intervention programs varies, ranging from, at minimum, the provision of an educational

brochure containing information regarding the effects of MTBI (e.g., Ref. 179) to a more comprehensive intervention program that couples educational material with various forms of treatment (e.g., access to a multi-disciplinary outpatient brain injury program; e.g., Ref. 180) and/or assessment (e.g., neuropsychological; e.g., 181)<sup>10</sup>. Providing educational information is a standard component in the majority of studies. Although the content of the educational sessions varies, these sessions typically aim to provide information regarding common symptoms, likely time course of recovery, reassurance of recovery, and suggested coping strategies following MTBI (e.g., Refs. 185–188). The mode of information dissemination ranges from the distribution of written information alone (e.g., 187) to providing written educational material and a discussion of its contents with a neuropsychologist (e.g., 180).

Research focusing on intervention following MTBI can be classified into three types of studies: (a) studies that treat MTBI patients with persistent symptoms many months post-injury, (b) studies that compare MTBI patients assigned to an intervention program versus a control group, and (c) studies that compare the efficacy of different types of intervention programs.<sup>11</sup> Two studies have evaluated the effectiveness of intervention programs for MTBI patients experiencing persistent problems. Ho and Bennet (189) reported that patients participating in a comprehensive brain injury treatment program had improved activities of daily living, neuropsychological test scores, and ratings on behavioral scales. Cicerone et al. (190) reported that 50 percent of patients who participated in a comprehensive brain injury program could be classified as having a good outcome (defined as resumption of pre-injury activities or other similar productive activity), improved scores on neuropsychological measures, and a reduced frequency of self-reported post-concussion symptoms following treatment. However, these two studies have been criticized by Paniak and colleagues for two reasons. First, they lack the inclusion of a control group that prevents ruling out explanations for improvement other than treatment. Second, they include patients who are first seen many months post-injury (and in some cases years), reducing the likelihood that patients are being treated for symptoms resulting from MTBI versus pre-existing disorders or co-morbid conditions (see 180 for a further discussion).

The majority of intervention studies compare patients assigned to a control group versus an intervention program within the first 1 to 3 weeks post-injury. In general,

<sup>10</sup>There are a few exceptions, with a handful of studies that have evaluated various interventions such as bed rest (182), hospital admission (183), and homeopathy (184).

<sup>11</sup>The first two types were conceptualized by Paniak et al. (180).

<sup>9</sup>Please see the chapter by Collins, Iverson, Gaetz, and Lovell in this book for a comprehensive review of outcome from sport concussion.

Z-SCORE	NORMAL	CONCUSSION: < 24 HR	CONCUSSION: 1-7 DAYS	CONCUSSION: > 7 DAYS	MTBI: 0-6 DAYS	MTBI: 7-30 DAYS	MTBI: 1-3 MONTHS	CANNABIS	LITIGATION	DEPRESSION	ADULT ADHD	MODERATE- SEVERE TBI: 0-6 MONTHS	MODERATE- SEVERE TBI: > 24 MONTHS	POOR EFFORT/ MALINGERING
1.6	90													
1.5	I						90							
1.4	I			90			I	90						
1.3	I			I			I	I						
1.2	80		90	I	90	I	I	I						
1.1	I		I	I	I	I	80	I	90	90				
1.0	I		I	80	I	I	I	80	I	I	90			
0.9	I		I	I	I	80	I	I	I	I	I			
0.8	I		80	I	80	I	I	I	I	I	I		90	
0.7	I		I	I	I	I	I	I	80	80	I		I	
0.6	50	90	I	I	I	I	I	I	I	I	80	90	I	
0.5	I	I	I	I	I	I	I	I	I	I	I	I	I	90
0.4	I	I	I	I	I	I	I	I	I	I	I	I	80	I
0.3	I	I	I	I	I	I	I	I	I	I	I	I	I	I
0.2	I	80	I	I	I	I	I	I	I	I	I	80	I	I
0.1	I	I	I	I	I	I	I	I	I	I	I	I	I	80
0.0	Average	I	I	I	I	I	I	I	I	I	I	I	I	I
-0.1	I	I	I	I	I	I	Average	I	I	I	I	I	I	I
-0.2	I	I	I	Average	I	I	I	Average	I	I	I	I	I	I
-0.3	I	I	I	I	I	Average	I	I	I	I	I	I	I	I
-0.4	I	I	Average	I	Average	I	I	I	I	I	I	I	I	I
-0.5	I	I	I	I	I	I	I	I	Average	Average	I	I	I	I
-0.6	50	I	I	I	I	I	I	I	I	I	Average	I	I	I
-0.7	I	I	I	I	I	I	I	I	I	I	I	I	I	I
-0.8	I	I	I	I	I	I	I	I	I	I	I	I	Average	I
-0.9	I	I	I	I	I	I	I	I	I	I	I	I	I	I
-1.0	I	Average	I	I	I	I	I	I	I	I	I	Average	I	I
-1.1	I	I	I	I	I	I	I	I	I	I	I	I	I	Average
-1.2	80	I	I	I	I	I	I	I	I	I	I	I	I	I
-1.3	I	I	I	I	I	I	80	I	I	I	I	I	I	I
-1.4	I	I	I	80	I	I	I	80	I	I	I	I	I	I
-1.5	I	I	I	I	I	80	I	I	I	I	I	I	I	I
-1.6	90	I	80	I	80	I	I	I	I	I	I	I	I	I
-1.7	I	I	I	I	I	I	90	I	80	80	I	I	I	I
-1.8	I	I	I	90	I	I	I	90	I	I	80	I	I	I
-1.9	I	I	I	I	I	90	I	I	I	I	I	I	I	I
-2.0	I	I	90	I	90	I	I	I	I	I	I	I	80	I
-2.1	I	I	I	I	I	I	I	I	90	90	I	I	I	I

-2.2	80		90	80	I	I
-2.3	I			I	I	80
-2.4	I			I	90	I
-2.5	I			I		I
-2.6	90			90		I
-2.7						90

**FIGURE 22-1**

Comparing the neuropsychological effects of MTBI to the normal population and other clinical groups: Distributions derived from meta-analyses.

*Note:* This figure illustrates, based on meta-analytic studies, the distributions of neuropsychological test performance across diagnoses, circumstances, or conditions. The shaded line in the middle represents the average score for healthy normal adults. 50 percent of healthy adults are expected to perform between the upper and lower shaded lines, and 80 percent of healthy adults are expected to perform between the solid lines. All groups are based on the theoretical normal distribution. The far left column represents z-scores (mean = 0, SD = 1). A z-score of  $-.67$  falls at the 25<sup>th</sup> percentile and  $.67$  falls at the 75<sup>th</sup> percentile. A z-score of  $-1.28$  falls at the 10<sup>th</sup> percentile and  $1.28$  falls at the 80<sup>th</sup> percentile. A z-score of  $-1.64$  falls at the 5<sup>th</sup> percentile and  $1.64$  falls at the 95<sup>th</sup> percentile. Deviations from the normal distribution are based on the effect sizes reported in the meta-analyses. For example, for MTBIs that are 1–3 months post injury, the effect size reported in the literature was  $.12$ . Therefore, the “Average” score for that group was dropped one position from the mean of zero, and the spread of scores was then centered around that average score. Effect sizes typically are expressed in pooled, weighted standard deviation units. However, across studies, there are some minor variations in the methods of calculation. By convention, effect sizes of  $.2$  are considered small,  $.5$  medium, and  $.8$  large. This is from a statistical, not necessarily clinical, perspective. For this figure, the overall effect on cognitive or neuropsychological functioning is reported. Sport concussion < 24 hr, 1–7 days, and >7 days, all in Belanger & Vanderploeg (4); MTBI 0–6 days, 7–29 days, 30–89 days, moderate-severe TBI 0–6 months, >24 months, all in Schretlen & Shapiro (8), Cannabis (411); Depression (412); Litigation/financial incentives (339); ADHD (413), based on Full Scale IQ, 123 studies; Exaggeration/Malingering (414).

researchers have reported favorable outcomes. Patients participating in intervention programs consisting of educational materials plus various additional treatments and/or assessments (e.g., neuropsychological testing, meeting with a therapist, reassurance, access to a multidisciplinary team) report fewer post-concussion symptoms at 3 months post injury (181, 187) and at 6 months post injury (177, 185, 188) compared to patients who received standard hospital treatment. However, not all research has been as favorable. Some researchers have reported that early intervention programs using educational material alone and educational material plus access to a specialist outpatient brain injury team, did not result in reduced self-reported post-concussive symptoms in children 3 months post injury (179) and adults 6 months post injury (191).

Although the majority of the research in this area points towards the usefulness of early intervention programs, our understanding of the *type* of intervention required is limited. The intervention programs evaluated in the literature to date vary considerably, ranging from economical programs (e.g., distribution of written educational materials) to much more expensive programs (e.g., multidisciplinary brain injury programs). Few studies have attempted to evaluate different intervention programs. In one of the first studies of this kind, Alves, Macciocchi, and Barth (192) compared the outcome of patients provided with standard hospital treatment to two different intervention programs provided within the first week post-injury: (a) education only, and (b) education and reassurance. Alves and colleagues concluded that intervention assignment was not associated with the number or duration of self-reported post-concussive symptoms at 3, 6, or 12 months post-injury.

In a more recent study, Paniak and colleagues compared patients assigned to two different treatment modes: (a) single session (i.e., a brief, educational and reassurance oriented session) and (b) treatment as needed (i.e., including education, reassurance, psychological, personality, and neuropsychological testing and feedback, consultation with physical therapist, and access to multidisciplinary brain injury treatment program as needed). Paniak and colleagues concluded that the brief educational and reassurance oriented intervention was as effective as the more comprehensive and expensive treatment model. There was no difference between the two interventions in self-reported post-concussive symptoms at 3 months and 12 months post-injury (180, 186).

The research focusing on early intervention is promising. However, this research is certainly not without its methodological problems. Some of the more serious problems include (a) the differences in definition of MTBI used across studies, and (b) the high attrition rate of patients belonging to the “intervention” group. Nonetheless, the literature suggests that early intervention

can be useful in this population by reducing the number of individuals who experience long term symptoms post-injury. In addition, and perhaps more importantly, research by Paniak and colleagues suggests that early intervention programs need not consist of complex multidisciplinary brain injury treatment programs, but may consist of a simple education session provided soon after injury. This is a conclusion echoed by Borg et al. (16) in their review of interventions for people with MTBIs. The effective use of simple education-oriented programs is supported in the literature (e.g., 181, 187). Future researchers are encouraged to (a) evaluate different treatment models in an effort to replicate the findings by Paniak and colleagues, (b) develop methods to minimize attrition rates, and (c) use “gold standard” definitions for selecting patients with MTBIs.

## RETURN TO WORK

Vocational outcome following traumatic brain injury is important for individual patients and society as a whole (193–197). For many individuals, the inability to return to work can result in a number of economic, social, family, and interpersonal problems (198–200). In addition, the economic burden placed on society is of concern (e.g., long-term sickness benefits, unemployment benefits), particularly because many individuals who sustain a TBI tend to be young and have their whole working lives ahead of them (196).

Some researchers have reported that injury severity, as measured by post-traumatic amnesia, loss of consciousness, and/or Glasgow Coma Scale scores, is associated with the time in which individuals return to pre-injury employment following TBI (e.g., 194, 197, 201, 202). However, other studies have failed to support the relation between injury severity and post-injury employment status (e.g., 203–207).

Despite these inconsistencies, individuals who have sustained an MTBI have consistently higher return to work rates when compared to individuals who have sustained a moderate or severe TBI (e.g., 197, 198, 208–211). However, not all individuals who have sustained an MTBI return to work at the same rate. Within the spectrum of MTBI, those individuals with lesser injuries (e.g., GCS = 15; no LOC) tend to have a higher return to work rate compared to those with more significant injuries (e.g., GCS = 13–14; with LOC; e.g., 101, 212, 213).

Return to work rates following MTBI vary substantially in the research literature. Post-injury employment rates have ranged from (a) 25 percent to 100 percent within the first month post-injury (e.g., 101, 198, 200, 214), (b) 38 percent to 83 percent six to nine months post-injury (147, 198, 199, 212, 215, 216), (c) 47 percent to

83 percent one to two years post-injury (141, 198, 209, 211), and (d) 62 percent to 88 percent three or more years post-injury (193, 197, 208, 209, 213). The literature regarding return to work following MTBI is summarized in Table 22-9.

The variability in return to work rates is likely due to the many methodological differences between studies. The most problematic of these include (a) differences in definitions of return to work (e.g., return to pre-injury employment vs. return to meaningful activity), (b) variations in the definition of MTBI (e.g., inclusion of GCS = 15 only versus GCS = 13–15), (c) variations in the inclusion and exclusion of individuals who were unemployed or performing domestic duties pre-injury in the sample, and (d) the failure of some studies to take into account pre-injury employment status (e.g., return to full time vs. part time vs. unemployed). For a comprehensive discussion regarding return to work following TBI, the interested reader is referred to the chapter by West and colleagues in this book.

Under most circumstances, we should anticipate good recovery and return to work following an MTBI. Patients should be reassured, and health care providers can work with injured adults to address the difficulties they face with particular symptoms while they resume their normal daily activities (e.g., work or school). Unfortunately, some trauma patients transition from acute postconcussion symptoms and problems into a mild depression (or major depressive episode). In people who transition, it might not be possible to determine if their primary diagnosis is depression or postconcussion syndrome. Basic and clinical research is needed in this area. Although the neuropathophysiology might be difficult to describe, the condition might be amenable to pharmacological and psychological intervention.

## DEPRESSION

Depression is common following traumatic brain injury of *all severities* (see 217 for a review). Prevalence estimates vary widely (e.g., from 11 percent to 77 percent; e.g., 218, 219, 220). In epidemiological studies, 11 percent to 21 percent of people with a history of TBI also have depression (e.g., 218, 221). In studies based on admissions to trauma centers or rehabilitation hospitals (222–227) or large samples of outpatients (228, 229) the rates of depression typically range from 14 percent to 42 percent. Recent well-controlled studies have concluded that depression occurs frequently in the first year post injury (224, 225), with rates decreasing over time (224, 230). Researchers have often reported that people who suffer traumatic brain injuries have higher rates of pre-injury psychiatric disorders (219, 231–233), such as depression and substance abuse.

Hibbard and colleagues (233) assessed 188 community-dwelling adults with *moderate to severe* traumatic brain injuries in a longitudinal cohort study. On average, the patients were evaluated 2.5 years post injury and then approximately 12 months later. The authors reported that 48 percent did not meet criteria for a major mood disorder at time one or time two, 29 percent were diagnosed with major depression at time one which resolved by time 2, 10 percent had late-onset depression (diagnosed at time 2 but not at time 1), and 14 percent had chronic depression (diagnosed at both time periods).

Depression is a heterogeneous condition. It can be a secondary or tertiary condition associated with traumatic brain injury, or it can be unrelated to the original brain injury. Researchers have speculated that depression can arise directly or indirectly from the biological consequences of the traumatic brain injury, it can be a psychological reaction to deficits and problems associated with having a brain injury, or both. A constant theme in the professional and scientific literature is that there are many methodological differences and scientific limitations across studies that make it very difficult to understand the prevalence, etiology, and natural history of depression in people with traumatic brain injuries. Moreover, most of the literature (as described in the previous paragraphs) relates to depression following *moderate or severe* traumatic brain injury. A review of prevalence studies relating to depression in people with MTBIs is presented in Table 22-10.

When patients report symptoms and problems many months after an injury, differential treatment often flows from differential diagnosis. Given the clear overlap between the symptoms of depression and postconcussion syndrome, some researchers have recommended treatment with antidepressants (e.g., 148, 234–236) or cognitive behavior therapy (e.g., 185, 237). Medications and psychotherapy would be an obvious choice, of course, if depression is simply mimicking the postconcussion syndrome. Those recommending cognitive behavior therapy have set forth a treatment protocol that is based on CBT principles but is tailored toward the postconcussion syndrome and belief systems relating to symptoms and brain damage.

Certainly, depression is relatively common in patients with traumatic brain injuries, although it is not necessarily more common in these patients than in patients with general trauma (227). The presence of depression in a person with a history of traumatic brain injury presents an obvious challenge if one attempts to diagnose a persistent postconcussion syndrome given the overlap in symptoms. Iverson (238) reported very high rates of possible *misdiagnosis* of persistent postconcussion syndrome in patients with depression. Participants were 64 physician-diagnosed inpatients or outpatients with depression who had independently-confirmed diagnoses on the Structured



**TABLE 22-9**  
*Summary of Return to Work Rates in the Research Literature*

FIRST AUTHOR	SETTING	N	COUNTRY	TIME POST-INJURY	PERCENT RTW	MTBI DEFINITION	RTW DEFINITION	PRE-INJURY WORK STATUS: INCLUSION/EXCLUSION CRITERIA	TYPE OF STUDY AND REFERRALS
Stranjalis (2004)	HTC <sup>1</sup>	100	Greece	1 wk	84 percent	GCS = 15 PTA < 15 min LOC < 15 min	Return to work/activities	Included = students, homemakers, retired, and unemployed.	Consecutive <sup>2</sup> Prospective
Wrightson (1981)	HTC	66	New Zealand	1 wk	81.8 percent <sup>3</sup>	Described as "Minor HI" (however, 2 patients had PTA 18–36hrs). No GCS or LOC data reported.	Return to work i.e., no longer had to take days off work.	All patients in regular employment at the time of injury	Consecutive Prospective
Wrightson (1981)	HTC	66	New Zealand	2 wk	92.4 percent <sup>3</sup>	Described as "Minor HI" (however, 2 patients had PTA 18–36hrs). No GCS or LOC data reported.	Return to work i.e., no longer had to take days off work.	All patients in regular employment at the time of injury	Consecutive Prospective
Haboubi (2001)	RC	391	UK	2 wk	44 percent	GCS = 13–15	Return to regular employment	Included those only in regular employment	Consecutive Retrospective
Dikmen (1994)	LITC	213	USA	1 mth	25 percent	GCS = 13–15	Return to work irrespective of length of that employment	Excluded = students, homemakers, and retired; Included = Workers <sup>4</sup> (Employed & Unemployed).	Consecutive Prospective Longitudinal
Wrightson (1981)	HTC	66	New Zealand	1 mth	99 percent <sup>3</sup>	Described as "Minor HI" (however, 2 patients had PTA 18–36hrs). No GCS or LOC data reported.	Return to work i.e., no longer had to take days off work.	All patients in regular employment at the time of injury	Consecutive Prospective

van der Naalt (1999)	HTC	43	Netherlands	1 mth	39 percent	GCS = 13–14	Resumption of previous activities either partially or completely.	None	Consecutive Prospective
Stranjalis (2004)	HTC	100	Greece	1 mth	99 percent	GCS = 15 PTA < 15 min LOC < 15 min	Return to work/activities	Included = students, homemakers, retired, and unemployed.	Consecutive Prospective
Haboubi (2001)	RC	391	UK	6 wk	88 percent	GCS = 13–15	Return to regular employment	Included those only in regular employment	Consecutive Retrospective
van der Naalt (1999)	HTC	43	Netherlands	3 mth	67 percent	GCS = 13–14	Resumption of previous activities either partially or completely.	None	Consecutive Prospective
Drake (2000)	NMC	121	USA	3 mth	53.7 percent	Described as “MTBI patients” but no specific criteria provided; LOC (M = 1.4 min, SD = 2.6 min); PTA (M = 3 hr, SD = 1.3 hr).	Return to full military duty defined by US Navy guidelines <sup>5</sup>	Included if in pre-injury active duty military status	Consecutive Prospective
Drake (2000)	NMC	121	USA	3 mth	100 percent	Described as “MTBI patients” but no specific criteria provided; LOC (M = 1.4 min, SD = 2.6 min); PTA (M = 3 hr, SD = 1.3 hr).	Return to full military duty defined by US Navy guidelines <sup>5</sup>	Included if in pre-injury active duty military status	Consecutive Prospective
McCullaugh (2001)	TTC	20	Canada	5 mth	37.5 percent	LOC < 20 mins PTA < 24 hr GSC 13–14	Return to previous work or studies	Excluded = retired, unemployed due to non-TBI injury; Included = employed, students, homemaker.	Consecutive Prospective
McCullaugh (2001)	TTC	37	Canada	5 mth	60 percent	LOC < 20 mins PTA < 24 hr GCS = 15	Return to previous work or studies	Excluded = retired, unemployed due to non-TBI injury; Included = employed, students, homemaker.	Consecutive Prospective

(continued)

TABLE 22-9 (continued)

FIRST AUTHOR	SETTING	N	COUNTRY	TIME POST-INJURY	PERCENT RTW	MTBI DEFINITION	RTW DEFINITION	PRE-INJURY WORK STATUS: INCLUSION/EXCLUSION CRITERIA	TYPE OF STUDY AND REFERRALS
Kraus (2005)	HTC	201	USA	6 mth	82.6 percent <sup>6</sup>	LOC < 30 mins GCS 13–15 PTA < 24 hr	No change in employment status post injury	Pre-injury work status not used to include/exclude patients.	Consecutive Prospective
Dikmen (1994)	LITC	213	USA	6 mth	63 percent	GCS = 13–15	Return to work irrespective of length of that employment	Excluded = students, homemakers, and retired; Included = Workers <sup>4</sup> (Employed & Unemployed).	Consecutive Prospective Longitudinal
van der Naalt (1999)	HTC	43	Nether-lands	6 mth	97 percent	GCS = 13–14	Resumption of previous activities either partially or completely.	None	Consecutive Prospective
Friedland (2001)	TTC	64	Canada	6–9 mth	44 percent	Initial GCS ≥ 13 PTA ≤ 24 hr LOC ≤ 30 min	Return to preinjury level or modified level.	Included all patients regardless of employment status.	Consecutive Prospective
Ruffolo (1999)	TTC	63	Canada	6–9 mth	42 percent <sup>7</sup>	GCS and LOC criteria used –LOC < 60 mins –GCS scores obtained but not reported.	Return to preinjury employment under usual or modified <sup>8</sup> conditions (paid or unpaid).	All working before the accident in paid or unpaid employment (e.g., students, volunteers, homemaker)	Consecutive Prospective
van der Naalt (1999)	HTC	43	Nether-lands	12 mth	100 percent	GCS = 13–14	Resumption of previous activities either partially or completely.	None	Consecutive Prospective
Dikmen (1994)	LITC	213	USA	12 mth	80 percent	GCS = 13–15	Return to work irrespective of length of that employment	Excluded = students, homemakers, and retired; Included = Workers <sup>4</sup> (Employed & Unemployed)	Consecutive Prospective Longitudinal
Dawson (2004)	TTC	38	Canada	1 yr	78.9 percent	GCS = 13–15	Return to productivity (i.e., paid employment and/or school)	Not described	Consecutive Prospective

van der Naalt (1999)	HTC	43	Netherlands	1 yr	79 percent	GCS = 13-14	Resumed previous activities completely	None	Consecutive Prospective
Dikmen (1994)	LITC	213	USA	2 yr	83 percent	GCS = 13-15	Return to work irrespective of length of that employment	Excluded = students, homemakers, and retired; Included = Workers <sup>4</sup> (Employed & Unemployed)	Consecutive Prospective Longitudinal
Dawson (2004)	TTC	24	Canada	4 yr	79.2 percent	GCS = 13-15	Return to productivity (i.e., paid employment and/or school)	Not described	Consecutive Prospective
Vanderploeg (2003)	USVV	373	USA	8 yr	75.1 percent	Described as MTBI with no reported LOC – No specific criteria presented.	Return to full time employment	Vietnam veterans who (a) had at least 4 months of active duty, (b) served only one tour of duty, (c) achieved a military occupation subspecialty other than “trainee” of “duty soldier”.	Consecutive Retrospective
Vanderploeg (2003)	USVV	253	USA	8 yr	81.8 percent	Described as MTBI + reported LOC – No specific criteria presented.	Return to full time employment	Vietnam veterans who (a) had at least 4 months of active duty, (b) served only one tour of duty, (c) achieved a military occupation subspecialty other than “trainee” of “duty soldier”.	Retrospective Random selected sample

(continued)

TABLE 22-9 (continued)

FIRST AUTHOR	SETTING	N	COUNTRY	TIME POST-INJURY	PERCENT RTW	MTBI DEFINITION	RTW DEFINITION	PRE-INJURY WORK STATUS: INCLUSION/EXCLUSION CRITERIA	TYPE OF STUDY AND REFERRALS
Asikainen (1996)	HOC	118	Finland	12 yr	61.9 percent	GCS = 13–15	Return to independent work only	No apparent exclusions based on work status	Retrospective Selected sample (patients with brain injury and post-injury problems in education and employment)
Asikainen (1996)	HOC	118	Finland	12 yr	72.9 percent	GCS = 13–15	Return to independent work or subsidized employment or education continuing	No apparent exclusions based on work status	Retrospective Selected sample (patients with brain injury and post-injury problems in education and employment)

Notes: <sup>1</sup>HTC = Hospital trauma center; RC = Rehabilitation clinic; LITC = Level 1 trauma center; NMC = U.S. Navel medical center; TTC = Tertiary trauma center; USVV = U.S. Vietnam veterans; HOC = Hospital outpatient clinic

<sup>2</sup>Consecutive = Consecutive referrals; Retrospective/Prospective = retrospective/prospective study design.

<sup>3</sup>A follow-up interview was obtained in 63 of the 66 patients 90 days post-injury regarding their condition on returning to work. Of these patients, 60 percent reported experiencing symptoms when they first returned to work and 46 percent reported that they were unable to do their work as well as usual.

<sup>4</sup>Workers were defined as individuals who defined themselves as “workers” regardless of whether they were employed or unemployed at the time of injury.

<sup>5</sup>Limited duty is a duty status within the military for individuals with ongoing medical problems; it has fewer responsibilities, some limitations, and decreased performance standards. Individuals are placed on limited duty for periods of six months, with the expectation of recovery and eventual return to full duty status” (p. 1106).

<sup>6</sup>It is not entirely clear whether this percentage includes individuals who were employed pre-injury, or also includes individuals who were retired, students, and unemployed.

<sup>7</sup>Of these patients, 12 percent returned to premorbid level of work and 30 percent returned to modified employment.

<sup>8</sup>Modified conditions was defined as “working shorter hr, performing lighter work, performing part of the job at home, or trading difficult tasks with other workers” (p. 393)

Sources: Asikainen, Kaste, & Sarna (208); Dawson, Levine, Schwartz, & Stuss (209); Dikmen, Temkin, Machamer, Holubkov, Fraser, & Winn (198); Drake, Gray, Yoder, Pramuka, & Llewellyn (216); Friedland & Dawson (215); Haboubi, Long, Koshy, & Ward (214); Kraus, Schaffer, Ayers, Stenehjem, Shen, & Afifi (199); McCullagh, Oucherlony, Protzner, Blair, & Feinstein (212); Ruffolo, Friedland, Dawson, Colantonio, & Lindsay (196); Stranjalis, Korfiatis, Papapetrou, Kouyialis, Boviatsis, Psachoulia, & Sakas (101); Uzzell, Langfitt, & Dolinskas (211); Vanderploeg, Curtiss, Duchnick, & Luis (213); van der Naalt, van Zomeren, Sluiter, & Minderhoud (141); Wrightson & Gronwall (200).

**TABLE 22-10**  
*Summary of Depression Prevalence Rates in MTBI*

FIRST AUTHOR	N	COUNTRY	POST-INJURY INTERVAL	SETTING	RATE OF DEPRESSION	MTBI DEFINITION	DEPRESSION DEFINITION	TYPE OF STUDY/ REFERRALS
Goldstein (2001)	18	USA	2 months	Acute care neurosurgery services affiliated with University hospitals	33 percent	GCS 13 to 15 LOC < 20 min Normal CT or MRI	GDS > 10	Prospective Consecutive
Mooney (2001)	80	USA	Median = 25.5 weeks	Rehabilitation Program, University hospital	44 percent	ACRM criteria	DSM-IV criteria	Prospective Selected Sample (individuals who failed to recover as expected 3 months post injury)
Levin (2005)	129	USA	3 months	Level I trauma center	11.6 percent	GCS 13 to 15	SCID: DSM-IV	Prospective Consecutive
McCauley (2001)	95	USA	3 months	Level I trauma center	21.4 percent	GCS 13 to 15 LOC < 20 mins Normal CT	DSM-IV Major Depressive Disorder criteria	Prospective Consecutive
Levin (2001)	60	USA	3 months	Level I trauma center	18.3 percent	GCS 13 to 15 LOC < 20 mins Normal CT	DSM-IV Major Depressive Disorder criteria	Prospective Consecutive
Horner (2005)	524	USA	12 months	State hospital	21.3 percent	<sup>1</sup> Injury to the head ICD/AIS = 2	“Since your injury, has a doctor told you that you had depression?”	Retrospective Random Selection of TBI
Parker (1996)	33	USA	M = 20 months	Private Practice/ Compensation	36 percent	Dx of “Whiplash” from medical records or on self description- excluded if LOC > 5 minutes or presence of cerebral abnormalities.	DSM-III-R	Prospective Selected Sample

Note: GDS = Geriatric Depression Scale; ACRM = American Congress of Rehabilitation Medicine (LOC < 30 mins, initial GCS = 13–15, PTA < 24 hr).

<sup>1</sup>TBI was defined as an injury to the head associated with decreased consciousness, amnesia, neurological abnormalities, skull fracture, or intracranial lesion, in accordance with the Centre for Disease Control and Prevention” (p. 323). TBI severity was determined by translating ICD-9-CM codes to ICD/AIS scores using ICDMAP-90 software” (p.324) Sources: Goldstein, Levin, Goldman, Clark, & Altonen (169); Horner, Ferguson, Selassie, Labbate, Kniele, & Corrigan (221); Levin, McCauley, Josic, Boake, Brown, Goodman, & Merritt (408); Mooney & Speed (409); McCauley, Boake, Levin, Contant, & Song (148); Parker & Rosenblum (410).

Clinical Interview for DSM-IV. These patients completed the British Columbia Postconcussion Symptom Inventory-Short Form (239, 240), a 16-item measure designed to assess the frequency and severity of symptoms based on ICD-10 criteria for postconcussion syndrome. Specific endorsement rates of postconcussion-like symptoms ranged from 31 percent to 86 percent for symptoms rated mild or greater, and from 11 percent to 58 percent for symptoms rated moderate-to-severe. Approximately 9 out of 10 patients with depression met liberal self-report criteria for a postconcussion syndrome and more than 5 out of 10 met conservative criteria for the diagnosis (in the absence of a previous MTBI). Depression is also common in persons with chronic pain (241, 242), and it is associated with increased disability in these patients (243, 244). Chronic pain is a frequent co-morbidity with depression (245–247). Therefore, patients seen long after a mild traumatic brain injury who have chronic pain, depression, or both are very likely to meet diagnostic criteria for a persistent postconcussion syndrome, even if the problems associated with the mild traumatic brain injury have long-since resolved.

### Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD; 248) occurs in some people who experience *intense fear, helplessness, or horror* during or immediately after experiencing or witnessing a traumatic event (except when “delayed”). Symptom onset typically occurs in the first few days (in fact the first 24 hr) in most people. The traumatic event is *persistently re-experienced* through (a) intrusive and distressing recollections of the event including visual images, thoughts, or perceptions; (b) distressing dreams (nightmares), (c) acting or feeling as if the traumatic event was happening again (e.g., dissociative flashbacks); (d) intense psychological distress when exposed to things (e.g., thoughts or external visual reminders) that symbolize or resemble an aspect of the event; or (e) physiological reactivity when exposed to things that symbolize or resemble an aspect of the traumatic event. In addition to the persistent re-experiencing, there is *persistent avoidance* of things associated with the traumatic event and a numbing of general responsiveness. Examples of avoidance and numbing of responsiveness include: (a) avoiding thoughts, feelings, or conversations associated with the event; (b) avoiding activities, places, or people that stimulate thoughts or memories of the event; (c) feeling detached or estranged from others; or (d) having a sense of a foreshortened future (e.g., not expecting to have a career, marriage, children, or a normal life span). In addition, the person has persistent symptoms of *increased arousal* such as (a) difficulty falling or staying asleep; (b) irritability or outbursts of anger; (c) difficulty concentrating; (d) hypervigilance; and (e) an exaggerated startle response. If a person meets criteria after one-month post event, PTSD is diagnosed.

Developing PTSD following a car accident is uncommon. Some estimates of the rate of this disorder in accident victims have been 9 percent (249), 12 percent (250), and 6.3 percent and 8.8 percent for men and women respectively (251). Essentially, 90 percent of people in car accidents do not develop PTSD. For comparison, less than 5 percent of individuals develop PTSD after a natural disaster (251). In a sample of survivors of the September 11, 2001 terrorist attack on the Pentagon, 14 percent had PTSD 7 months after the event (252). Sexual assault is associated with the highest incidence of PTSD, with estimates ranging from 46 percent to 80 percent (250, 251).

Patients with PTSD often report the same symptoms as patients who have sustained MTBIs. For example, in a sample of 128 patients with PTSD, 89 percent reported irritability, 56 percent reported memory problems, 92 percent reported concentration problems, and 90 percent reported difficulty sleeping (253). A controversial and confusing issue is whether a person who sustains a traumatic brain injury can develop PTSD. There are data to support the position that MTBI and PTSD typically are mutually exclusive (254–256), although researchers have put forward a compelling rationale for how, under certain circumstances, PTSD could emerge in a patient with a brain injury (257, 258). The conceptual question at the heart of the debate is whether a person with no memory for a traumatic event can develop PTSD. In other words, how can you be traumatized by an event you can't remember? How can you re-experience, through flashbacks, images, or dreams, an event you cannot remember? Some mechanisms might include islands of memory of traumatic events occurring outside of the amnesic gap (such as gaining awareness in the hospital with a tracheotomy in and on a ventilator), or so-called elaborative cognitions.

A recent, well-controlled study provides additional information to better understand this issue. Gil and colleagues prospectively studied 120 accident victims who sustained a mild traumatic brain injury and who were hospitalized for observation immediately after their trauma. They were assessed within the first 24 hr and at one week, three months, and six months. At 6 months post-injury, 14 percent met diagnostic criteria for PTSD. Predictors of PTSD at 6 months were (a) PTSD symptoms, depressive symptoms, and anxiety symptoms at one week post-injury, (b) history of psychiatric disorder, and (c) memory for the event. Of the patients with memory for the event, 13/55 (23 percent) had PTSD at 6 months post-injury, compared to only 4/65 (6 percent) who did not have memory for the event (259). Therefore, the literature to date suggests quite clearly that having no memory for the event likely protects the individual from developing PTSD.

Clinicians should be very cautious in diagnosing PTSD in a person who has sustained an MTBI if that

person does not exhibit prominent symptoms in the initial days post injury. The onset of symptoms in PTSD generally is rapid. For example, the onset of PTSD symptoms in the survivors of the Oklahoma City bombing was swift, with 76 percent reporting symptoms on the day of the event (260). Delayed symptom onset is very uncommon. For example, there were no cases of delayed onset PTSD associated with the Oklahoma City bombing (261, 262) or a mass shooting incident (263, 264). Delayed onset PTSD, in the vast majority of studies, has been considered rare (e.g., 265–267). Therefore, if delayed onset phenomena appear, they might be a joint product of (a) insensitive diagnostic criteria and methods, (b) individual differences in avoidance behavior that masks other PTSD symptoms, (c) post-trauma stressors that exacerbate psychological distress, and/or (d) delayed compensation motivation (265, 268). As illustrated in the study by Gil and colleagues, patients with MTBIs are likely at increased risk for developing PTSD if (a) they have a psychiatric history, (b) they have memory for the event, and (c) they develop major symptoms within the first 24 hr or first week post injury (259).

### RISK FOR ALZHEIMER'S DISEASE

There has been considerable research interest regarding whether mild, repetitive mild, moderate, or severe traumatic brain injuries increase a person's risk for developing Alzheimer's disease (AD). Before discussing this literature, it is important to consider the broader literature on risk for AD. Without question, the biggest risk factor for AD is age. Living longer greatly increases one's chance of developing the disease. Several meta-analytic studies have consistently found that the prevalence of AD around the world increases with age (e.g., 269–272). In an early meta-analysis of 22 studies, Jorm and colleagues (270) reported that the prevalence of AD doubled every 4.5 years; they reported the following prevalence rates stratified by age group: 65–69 years (1.4 percent), 70–74 years (2.8 percent), 75–79 years (5.6 percent), 80–84 years (11.1 percent), and 85 years or more (23.6 percent). Using the United States census data, Hebert and colleagues estimated that in 2000 4.5 million persons in the United States had AD, and by the year 2050 this figure will triple to 13.2 million due to the ageing population (273).

An overview of the recent literature reveals considerable scientific interest in many other potential risk factors, such as genetics (274), particularly the apolipoprotein E (ApoE) gene (275, 276); genetics and a high fat diet (277); oxidative stress, disturbed protein metabolism, and their interaction (278, 279); zinc metabolism (280); cerebrovascular disease and vascular risk factors (281, 282); cardiovascular disease, particularly in the subgroup with peripheral arterial disease (283); high cholesterol (284),

elevated plasma total homocysteine concentrations and low serum folate concentrations (285); midlife obesity (286); loss of microglial cell function (287); decreased melatonin (288); heavy metal exposure (289); and lack of exercise (290). The risk of AD appears to increase with the number of vascular risk factors (diabetes + hypertension + heart disease + current smoking), with diabetes and current smoking being the strongest risk factors in isolation or in clusters in a recent study (291). Mental health problems, such as a history of depression in adulthood (292), particularly for men (293), have been associated with an increased risk for AD. Even a man's height has been associated with risk for AD! Short men are at increased risk (presumably due to its association with childhood nutrition and other risk factors for dementia) (294). Watching too much television in middle-adulthood has been associated with an increased risk for AD, presumably as a marker for reduced participation in intellectually stimulating activities (295).

For the past 20 years there has been considerable interest in the relation between traumatic brain injury and the future development of AD. It has been suggested that traumatic brain injuries reduce "cognitive reserve," resulting in increased vulnerability to developing the disease (296). The animal literature has revealed evidence that some of the pathological features of AD arise shortly after traumatic brain injury (see 297 and 298 for reviews), and human autopsy studies also have supported these findings (299, 300). A number of studies have reported a relation between a history of traumatic brain injury and a current diagnosis of AD (e.g., 301–314), although several studies have failed to find this association (e.g., 315–323). Mortimer and colleagues conducted an important meta-analytic review of the literature published prior to 1991 (324). They reported that traumatic brain injuries were associated with a 1.82 relative risk (RR) (95 percent confidence interval = 1.26 to 2.67) for developing AD. The relative risk was significant for men (RR = 2.67, 95 percent CI = 1.64 to 4.41) but not women (RR = 0.85, 95 percent CI = 0.43 to 1.70). Fleminger and colleagues conducted a second meta-analytic review of the literature, published in 2003, and reported that the literature published since 1991 did *not* reveal a statistically significant increased risk for AD (325). However, the literature as a whole (i.e., the studies published before and after the Mortimer meta-analysis) did reveal an increased risk for AD associated with a history of TBI (Odds Ratio (OR) = 1.58, 95 percent CI = 1.21 to 2.06). Again, the increased risk was significant for men (OR = 2.26, 95 percent CI = 1.13 to 4.53) but not women (OR = 0.92, 95 percent CI = 0.53 to 1.59). Starkstein and Jorge (326) suggested that this increased risk in men and not women might simply reflect men getting more severe traumatic brain injuries. Jellinger, in his review of the literature, emphasized that



epidemiological and autopsy studies have provided evidence of an association between *severe* traumatic brain injury and AD, but the relationship between AD and brain injury and apolipoprotein E status is still ambiguous (298). Overall, there are many conflicting results in this large literature spanning more than 20 years. Nonetheless, it is reasonable to conclude that patients who sustain *severe* TBIs are at a small increased risk for developing AD, as concluded by Starkstein and Jorge (326) and Jellinger (298).

In conclusion, most prospective studies showed a significant, albeit weak, association between dementia and history of TBI. Some studies showed that a history of TBI may result in a relatively early onset of dementia, but this was not replicated by others. The association with the APOE-e4 allele status is conflicting as well, from one study showing a tenfold increase in the risk for dementia for individuals with both a history of TBI and APOE-e4, to another study showing an increased risk for dementia among those *without* an APOE-e4 allele. (p. 599; Ref. 326)

Given that (a) many studies have failed to find an association between history of TBI (of any severity) and AD, (b) the meta-analyses have only identified this association for men, (c) several studies have found a severity effect (i.e., risk is greater in patients with more severe brain injuries), and (d) the pathophysiology of MTBI, especially on the milder end of the spectrum of this injury, is temporary and reversible, it would be a mistake to assume, at this point in time, that patients with *MTBIs*, as a group, are at increased risk for AD. Several specific studies suggest that there is not a relationship between MTBI and risk for AD (e.g., 306, 310, 321).

## PERSISTENT POST-CONCUSSION SYNDROME

There is a so-called “miserable minority” (327) of patients who appear to have poor long-term outcome following a mild traumatic brain injury (MTBI). The etiology of the so-called *persistent* postconcussion syndrome has never been agreed upon (see 7, 328–330 for reviews). For decades, researchers have questioned the validity of this diagnosis as a true syndrome or disease entity (e.g., 331–336). Others have noted that the syndrome is rare in prospective studies (e.g., 192, 333), and concerns regarding the role of financial compensation on symptom reporting have been expressed for many years (331, 337–340). Most researchers simply suggest that the etiology is due to the biological effects of the injury, psychological factors, psychosocial factors (broadly defined), chronic pain, or a combination of factors (171, 341–348). Ruff and colleagues (327, 330, 349) have stressed a multidimensional cumulative stressor conceptualization of

the persistent post-concussion syndrome. Essentially, setbacks in several aspects of a person’s life (physical, emotional, cognitive, psychosocial, vocational, financial, and recreational) serve as cumulative stressors that interact with personality and premorbid physical and mental health factors, resulting in the syndrome. This model stresses the complexity of the etiology and maintenance of the syndrome.

Experienced clinicians and researchers know that it is extraordinarily difficult to disentangle the many factors that can be related to self-reported symptoms in persons who have sustained remote MTBIs (328). This is a challenging and potentially contentious diagnosis, of course, because post-concussion-like symptoms are common in healthy subjects (240, 350–355), in patients with no history of brain injury, such as outpatients seen for psychological treatment (356), outpatients seen for minor medical problems (357), personal injury claimants (357, 358), patients with post-traumatic stress disorder (253), patients with orthopedic injuries (332), individuals with chronic pain (359–362) and patients with whiplash (363). Thus, the differential diagnosis of the persistent post-concussion syndrome is very challenging.

## CONCLUSIONS

Mild traumatic brain injury, and the potential for incomplete recovery and poor psychosocial outcome, has been recognized as a public health problem (364–366). The pathophysiology of MTBI is predominately neurometabolic and reversible. However, this injury can be characterized by structural damage that is visible with static neuroimaging (e.g., CT or MRI; 17, 19–24) and cellular damage that is not visible through neuroimaging (80) in some people.

Despite decades of research, slow or incomplete recovery from MTBI is poorly understood. For a substantial majority of people, MTBIs are self-limiting and generally follow a predictable course. Permanent cognitive, psychological, or psychosocial problems due to the biological effects of this injury are relatively uncommon in trauma patients and rare in athletes (4, 6–9).

However, some people do not appear to recover completely following this injury; these individuals have been referred to as the “miserable minority” (173, 327, 328). Some have estimated that 10–20 percent of people with MTBIs will have incomplete recovery (e.g., 173, 367), although this figure is likely an over-estimate (7). When a person does not recover quickly, health care providers are very concerned about the possibility of a persistent postconcussion syndrome (328, 329, 341, 342, 345, 346), the development of depression (see 217 for a review), and/or a failure to return to work (101, 141, 147, 193, 197–200, 208, 209, 211–216). The underlying cause

for poor outcome in a minority of patients is likely multifactorial, and could involve combinations of factors such as pre-existing personality characteristics, life stress, psychiatric conditions, or substance abuse problems (140, 330, 368); co-morbid conditions, such as chronic pain, depression, PTSD, life stress, or substance abuse (148, 359, 361, 362, 369–371); structural damage (macroscopic and microscopic) to the brain (11, 146); litigation (338, 340, 372); exaggeration or malingering (373–377); and symptom expectations, misattribution, and response bias (352, 370, 378–383).

Health care providers should try to prevent or reduce the severity of symptoms and problems that extend beyond a few weeks or months post injury. Early identification and intervention, with education and reassurance of the likelihood of a good outcome, to ameliorate anxiety and facilitate adjustment to transient impairment, is a recommended treatment for persons with MTBIs. Most researchers (177, 180, 181, 185–188) but not all (179, 191) have reported very favorable outcomes in studies on early intervention following MTBI.

Health care providers should be cautious when diagnosing someone with a persistent postconcussion syndrome, because this implies directly or indirectly that the person has “permanent brain damage.” This can be a relief to some patients as an explanation for their perceived problems or it can have serious iatrogenic implications for other patients, a so-called “nocebo effect.” This might promote a preoccupation with symptoms, fear of permanent brain damage, with hypochondriacal concern and adoption of a sick role (as per the ICD-10 diagnostic criteria for the postconcussion syndrome). For those with persistent problems, differential treatment often flows from differential diagnosis. Given the clear overlap between the symptoms of depression (and PTSD) and post-concussion syndrome, some researchers have recommended treatment with antidepressants (e.g., 148, 234–236) or cognitive behavior therapy (e.g., 185, 237). Those recommending cognitive behavior therapy have provided a treatment protocol that is based on CBT principles but is tailored toward the post-concussion syndrome and belief systems relating to symptoms and brain damage.

It will not be possible to significantly advance our understanding of poor outcome in people with MTBIs without multidisciplinary and multimodal research. This includes psychosocial and psychological research (e.g., symptom expectations and attributions), functional imaging studies, as well as differential diagnoses and specificity studies (e.g., direct comparisons with patients who have problems with depression, anxiety, substance abuse, or ADHD). Much more research is needed regarding the sensitivity and specificity of structural and functional neuroimaging techniques for trauma patients who have poor outcome from MTBI. Researchers should consider the broader neuroimaging literature in biological psychiatry.

This is because depression, chronic pain, PTSD, alcoholism, and ADHD are associated with abnormalities on SPECT (384, 385), PET (386–389), fMRI (387, 389–391), MR spectroscopy (392–396), and quantitative structural imaging (397–405). Therefore, trying to isolate imaging findings that are *specific* to the long-term effects of an MTBI should occur in the greater context of studying similar abnormalities associated with possible co-morbid conditions (e.g., depression, chronic pain, or substance abuse) or other mitigating factors.

The ability for patients with MTBIs to be properly diagnosed and treated will be greatly enhanced by three major and likely developments in the field of brain injury medicine. First, we need to develop and implement a system of standardized international terminology and classification for the condition. Second, we need to advance neurodiagnostic technology that facilitates the diagnosis of persistent cerebral functional impairment due to MTBI with high levels of sensitivity and specificity. Finally, we need to enhance our understanding of how pre-injury, injury, and post-injury vulnerability factors can affect functional outcome and can be accommodated for in the context of treatment planning. Although there is still much that we have to learn about the condition of MTBI, we have made significant progress and further progress will clearly lead to both better diagnostic accuracy and better neurological as well as functional outcomes.

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# 23

## Post-Concussive Disorder

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### INTRODUCTION

A concussion, by definition, is a mild traumatic brain injury (MTBI). MTBIs are expected to be self-limiting and to follow a predictable course. Permanent cognitive, psychological, or psychosocial problems due to the biological effects of this injury are relatively uncommon in trauma patients and rare in athletes (1–6 and see chapters by Collins et al. and Iverson et al. in this book). However, some people do not appear to recover well following MTBI; these individuals have been referred to as the “miserable minority” (7, 8). When a person does not recover quickly, health care providers may be very concerned about the possibility of a persistent post-concussive disorder (9–14), the development of depression (see 15 for a review), and/or a failure to return to work (16–28), among other potential complications.

The post-concussive disorder is one of the most controversial syndromes/disorders in medicine and psychology. In medicine, we consider a syndrome a group of signs and symptoms that collectively indicate or characterize a disease, psychological disorder, or abnormal condition. The signs and symptoms of a syndrome are believed to have a common cause. It is widely believed that 10–20% of people who sustain an MTBI will develop a more persistent form of the syndrome (i.e., lasting one or more years). A 15% prevalence of poor outcome has been cited

frequently over the past 25 years based on the results from a prospective study in the mid 1970s by Rutherford and colleagues. These researchers followed consecutive admissions to the hospital for MTBIs and reported that 14.5% of patients had *at least one* symptom at one-year post-injury. However, fewer than 5% had multiple (four or more) symptoms. This figure is never cited. Moreover, the authors’ concerns about the validity of the syndrome have been lost over the years, and only the “15%” figure has been retained.

It is probably the multiplicity and the diversity of complaints which has given the term ‘post-concussion syndrome’ such widespread acceptance. However, of the 19 patients who complained, 6 had only 1 symptom and a further 7 had 2. The remaining 6 had between 4 and 9 symptoms. In a syndrome one expects groupings of inter-related symptoms. We found no such groupings either at 6 weeks or at 1 year (Ref. 29; p. 228).

The widely-cited estimate of 10–20% of patients suffering a long-term post-concussive disorder is both confusing and incorrect. It is confusing because there is often an assumption that if a person reports symptoms long after an MTBI, that the symptoms are causally-related to the biological effects of the injury (by logical inference, the symptoms are related to damage to the

structure or function of the brain). It is incorrect because the constellation of symptoms comprising the post-concussive disorder likely occurs in far less than 10–20% of patients with remote MTBIs. Moreover, there are numerous potential underlying causes for these symptoms that are unrelated to traumatic brain damage.

If we consider *all* MTBIs, the percentage of people with poor long-term (e.g. greater than one year) outcome is likely very small (i.e., clearly less than 5%). This is because the definition of concussion, as it is generally defined, is so broad that a person simply needs to feel momentarily dazed, and unwell for a brief period of time, to meet criteria. A mild injury to the brain is common in daily life and in sports. Those injuries on the milder end of the “mild” spectrum, as a rule, do not result in biologically-based symptoms and problems that last beyond a few minutes, days, or weeks. For example, a substantial minority of amateur and professional athletes who sustain a concussion have no residual symptoms or problems after a few hours or a single day; and 90% of concussed university football players appeared recovered in 7 days (30). In a recent, large-scale prospective study with high school football players, approximately 90% were recovered within the first month post-injury (31). Although it is possible for an athlete to have a persistent post-concussive disorder, and we occasionally see these athletes in clinical practice, the incidence of this syndrome/disorder in athletes is extremely low (of course, far less than a 15% estimate of poor outcome at one-year post-injury).

The estimates that 10–20% of patients have poor outcome, and thus possibly a “persistent” post-concussive disorder, come from studies of trauma patients seen in the hospital, not athletes with MTBIs or civilians seen by their family doctors or in clinics. According to a US Census Bureau survey, more than 600 people per 100,000 sustain a brain injury with loss of consciousness each year (32). Of these people, 35% are seen in the emergency room, 25% are hospitalized, 14% are seen in doctors’ offices or clinics, and 25% seek no medical care. Historical prospective studies reporting poor outcome have been based on either the 25% of cases that are hospitalized or the 35% seen in emergency departments. In the past, these patient groups were broadly defined, in terms of injury severity, and likely included a subset of patients with complicated MTBIs or moderate TBIs. Researchers have reported that patients who agree to participate in prospective research on outcome from MTBI have more severe injuries than those who refuse participation (e.g., rate of CT abnormalities was 33% in participants and 6% in refusals; 33). Thus, the historical studies often began with a non-representative sample and then, due to attrition (severe in some studies), the final sample was highly non-representative. Moreover, in some studies patients were considered to have persistent problems if they endorsed

a single symptom (e.g., headaches or concentration problems) at one-year post-injury! In a large scale prospective study, Alves and colleagues (34) reported that at one year post-injury single symptoms were commonly experienced but multiple symptoms were “extremely rare” (2–6% of subjects).

There are other data suggesting that the disorder, or at least some persistent symptoms, might occur in *more* than 10–20% of people at one-year post-injury (e.g., 35–37). In general, studies involving the “persistent post-concussive disorder” should be reviewed carefully from a methodological perspective to determine (a) the representativeness of the sample, and (b) the criteria used to “diagnose” the disorder. Is the sample comprised of patients and litigants long after an injury who are referred to a specialty clinic? What are the criteria for assuming continuing symptoms arising from the original injury? Does the person need to report one, two, three, or more symptoms? That is, can the condition be considered syndromal in the absence of a threshold number of symptoms and/or signs? If there are a specific number of symptoms and/or signs that need to be present to reach a threshold for diagnosing the disorder, which ones should they be? That is, are there symptoms/signs that should be more heavily weighted than others based on them being more likely to be a biological consequence of the MTBI rather than arising from other etiologic factors? For example, in a prospective study conducted in Lithuania, if the disorder was defined as endorsing three or more symptoms at one-year post-injury, 78% of patients with mild traumatic brain injuries met criteria. However, in the same study, 47% of trauma control subjects, with no history of head or brain injury, met criteria for the persistent post-concussive disorder using the three or more symptoms criteria (38). These authors reported that if a constellation of six core symptoms were necessary to meet criteria for the diagnosis, then after 3 months, only 1% of patients with MTBIs and 1.4% of trauma controls would meet criteria for diagnosis. At one-year post-injury, only 0.5% of patients with MTBIs and 0.005% of trauma controls had this symptom combination. Therefore, a researcher or clinician can draw radically different conclusions from different data presented in the same study.

Despite decades of research, the incidence, prevalence, and etiology of the post-concussive disorder have never been established in a manner that would meet evidence-based medicine criteria. We believe that the post-concussive disorder can arise following a mild traumatic brain injury as a direct or indirect consequence of this injury. The “true” disorder is very much influenced by psychological factors (e.g., see 39), with varying degrees of underlying neurological or neurophysiological problems. The disorder can also be misdiagnosed because the symptoms are non-specific. There are numerous diverse factors that can influence how people perceive and report

their symptoms and functional problems long after a mild traumatic brain injury. The purpose of this chapter is to examine some of the more likely factors that may contribute to persistent and sometimes even permanent symptoms and problems following traumatic injuries that may (or may not) involve mild traumatic brain injury. The thesis of this chapter is that the post-concussive disorder is a non-specific cluster of symptoms that can be mimicked by a number of pre-existing or co-morbid conditions. The disorder, theoretically, also can occur in tandem with these conditions. Therefore, it is important to consider carefully the differential diagnosis of the disorder, in the hopes that differential diagnosis leads to differential treatment and rehabilitation, reduced patient suffering, and better functional outcomes. This chapter is divided into the following five sections: (a) diagnostic criteria, (b) differential diagnoses & co-morbidities, (c) iatrogenesis, (d) factors relating to the perception and reporting of symptoms, and (e) conclusions.

## DIAGNOSTIC CRITERIA

There are two current sets of research criteria for the post-concussive disorder: the International Classification of Diseases, 10th edition (ICD-10), and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). According to the ICD-10 (40), a person must have a history of “head trauma with a loss of consciousness” preceding the onset of symptoms by a period of up to 4 weeks and have at least three of six symptom categories. These include: (a) headaches, dizziness, general malaise, excessive fatigue, or noise intolerance, (b) irritability, emotional lability, depression, or anxiety, (c) subjective complaints of concentration or memory difficulty, (d) insomnia, (e) reduced tolerance to alcohol, and (f) pre-occupation with these symptoms and fear of permanent brain damage.

The syndrome occurs following head trauma (usually sufficiently severe to result in loss of consciousness) and includes a number of disparate symptoms such as headache, dizziness (usually lacking the features of true vertigo), fatigue, irritability, difficulty in concentrating and performing mental tasks, impairment of memory, insomnia, and reduced tolerance to stress, emotional excitement, or alcohol. These symptoms may be accompanied by feelings of depression or anxiety, resulting from some loss of self-esteem and fear of permanent brain damage. Such feelings enhance the original symptoms and a vicious circle results. Some patients become hypochondriacal, embark on a search for diagnosis and cure, and may adopt a permanent sick role. The etiology of these symptoms is not always clear, and both organic and psychological factors have been proposed to account them. The nosological status of this condition is thus somewhat uncertain. There

is little doubt, however, that this syndrome is common and distressing to the patient. Diagnostic Guidelines: At least three of the features described above should be present for a definite diagnosis. Careful evaluation with laboratory techniques (electroencephalography, brain stem evoked potentials, brain imaging, oculonystagmography) may yield objective evidence to substantiate the symptoms but results are often negative. The complaints are not necessarily associated with compensation motives (Ref. 40; section F07.2).

The specific research criteria for the Post-concussional Syndrome are set out in Table 23-1. Notice that the ICD-10 criteria do not require “objective” evidence of cognitive problems (in contrast to the DSM-IV criteria described later). The emphasis is on subjective cognitive complaints that are not, in fact, easy to document through neuropsychological testing. This, presumably, is to distinguish the diagnosis from the more serious injuries, conditions, and diseases affecting the brain that have more pronounced associated neurocognitive impairments. Also note that a person with “emotional changes, insomnia, and a pre-occupation with having brain damage” would meet diagnostic criteria for the syndrome. This definition incorrectly and implicitly “assumes” that numerous physical symptoms commonly considered secondary to MTBI are only associated with MTBI and do not have other etiologies, thereby implying a lack of need for adequate differential diagnosis of the cause of the various symptoms reported after traumatic injury.

The fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; 41) included research criteria for the Post-concussional Disorder (see 42, for an interesting discussion of the development and limitations of these criteria). According to these criteria, the individual must show objective evidence on neuropsychological testing of declines in some of his or her cognitive abilities, such as attention, concentration, learning, or memory. The person must also report three or more subjective symptoms from Category C, and these symptoms must be present for at least 3 months. The Category C symptoms are: (a) becoming fatigued easily, (b) disordered sleep, (c) headache, (d) vertigo or dizziness, (e) irritability or aggression on little or no provocation, (f) anxiety, depression, or affective lability, (g) changes in personality (e.g., social or sexual inappropriateness), and (h) apathy or lack of spontaneity. The DSM-IV includes the additional criteria: “The disturbance causes significant impairment in social or occupational functioning and represents a significant decline from a previous level of functioning.”

The essential feature is an acquired impairment in cognitive functioning, accompanied by specific neurobehavioral symptoms, that occurs as a consequence of closed head injury of sufficient severity to produce



**TABLE 23-1**  
**FO7.2 Post-Concussional Syndrome (Research criteria from the ICD-10)**

Note: The nosological status of this syndrome is uncertain, and criterion A of the introduction to this rubric is not always ascertainable. However, for those undertaking research into this condition, the following criteria are recommended:

- A. The general criteria of F07 must be met.  
(The general criteria for F07, Personality and Behavioral Disorders Due to Brain Disease, Damage and Dysfunction, are as follows: G1. Objective evidence (from physical and neurological examination and laboratory tests) and/or history, of cerebral disease, damage, or dysfunction. G2. Absence of clouding of consciousness and of significant memory deficit. G3. Absence of sufficient or suggestive evidence for an alternative causation of the personality or behavior disorder that would justify its placement in section F6 (Other Mental Disorders Due to Brain Damage and Dysfunction and to Physical Disease).
- B. History of head trauma with loss of consciousness, preceding the onset of symptoms by a period of up to four weeks (objective EEG, brain imaging, or oculonystagmographic evidence for brain damage may be lacking).
- C. At least three of the following:
- (1) Complaints of unpleasant sensations and pains, such as headache, dizziness (usually lacking the features of true vertigo), general malaise and excessive fatigue, or noise intolerance.
  - (2) Emotional changes, such as irritability, emotional lability, both easily provoked or exacerbated by emotional excitement or stress, or some degree of depression and/or anxiety.
  - (3) Subjective complaints of difficulty in concentration and in performing mental tasks, and of memory complaints, without clear objective evidence (e.g. psychological tests) of marked impairment.
  - (4) Insomnia.
  - (5) Reduced tolerance to alcohol.
  - (6) Preoccupation with the above symptoms and fear of permanent brain damage, to the extent of hypochondriacal over-valued ideas and adoption of a sick role.

a significant cerebral concussion. The manifestations of concussion include loss of consciousness, post-traumatic amnesia, and less commonly, post-traumatic onset of seizures. Specific approaches for defining this criterion need to be refined by further research. Although there is insufficient evidence to establish a definite threshold for the severity of the closed head injury, specific criteria have been suggested, for example, two of the following: 1) a period of unconsciousness lasting more than 5 minutes, 2) a period of post-traumatic amnesia that lasts more than 12 hours after the closed head injury, or 3) a new onset of seizures (or marked worsening of a pre-existing seizure disorder) that occurs within the first 6 months after the closed head injury (p. 760, DSM-IV-TR, Ref. 43).

Notice that the DSM-IV criteria require objective evidence of cognitive problems. The DSM-IV emphasizes that the “closed head injury” is sufficient to produce “a significant cerebral concussion.” As is often the case in the literature, there is an intermingling of terminology that lacks precision in this definition. In some places “closed head injury” seems to imply cranial trauma and in other places it is used analogously with MTBI. The injury severity markers provided as examples included loss of consciousness (LOC) greater than five minutes, post-traumatic amnesia (PTA) greater than 12 hours, or the new onset of seizures. Clearly, it was the intent of the authors to differentiate the MTBI believed to underlie this

disorder from very mild concussions often experienced in day-to-day life. This definition implies that the disorder should be considered uncommon in people who do not have these more significant injury severity markers, although some researchers have reported that these markers are not reliable predictors of the disorder (e.g., 44, 45). Ruff and Jurica (44) reported that subjective complaints and neuropsychological test performance did not differ in a sample of post-acute patients with mild traumatic brain injuries, of different severities within the mild spectrum, as might be expected if the DSM-IV criteria were predictive of outcome.

When the ICD-10 and DSM-IV criteria are compared in the same set of patients, large diagnostic differences emerge (46, 47). This is because the DSM-IV criteria requires (a) neurocognitive impairment, and (b) impairment in important role functioning. The ICD-10 does not have these “impairment” criteria. Researchers have reported that consecutive patients with mild traumatic brain injuries, seen at a Level I trauma center and followed prospectively, have relatively low rates of diagnosis at three months post-injury using the DSM-IV criteria (i.e., 11% to 17%) compared to the ICD-10 criteria (54% to 64%) (46, 47).

Ruff (7) proposed four modifiers for the Post-concussional Disorder. These modifiers are as follows: (a) PCD with objective neuropathological features, (b) PCD with neurocognitive features, (c) PCD with psychopathological features, and (d) PCD with neurocognitive and

psychopathological features. The PCD with objective neuropathological features classification identifies those patients with a combination of neuropsychological deficits and abnormalities identified on neuroimaging (i.e., those with “complicated” MTBIs). PCD with neurocognitive features is used if (a) a cluster of cognitive deficits consistent with MTBI are reliably documented on neuropsychological testing, (b) there is an absence of significant emotional overlay, and (c) there is an absence of positive neuroimaging. PCD with psychopathological features is used when (a) persistent emotional sequelae dominate the clinical picture (e.g., acute stress reaction, depression, panic attacks), (b) neuropsychological deficits are disproportionate with the duration of loss of consciousness or post-traumatic amnesia, and absence of neuroimaging findings, and (c) symptoms tend to persist or even worsen over time. PCD with neurocognitive and psychopathological features is used when there is a mixture of documented neurocognitive deficits and acquired emotional problems that demonstrate some improvements over time, and there is an absence of positive neuroimaging.

The most serious and obvious problem with the ICD-10 and the DSM-IV criteria for the post-concussive disorder is causally linking the subjective, self-reported symptoms to the original MTBI. In fact, the etiology of the so-called *persistent* post-concussive disorder has never been agreed upon (see 4, 12, and, 48 for reviews). For decades, researchers have questioned the validity of this diagnosis as a true syndrome or disease entity (e.g., 29, 38, 49–52). Others have noted that the syndrome is rare in prospective studies (e.g., 29, 34), and concerns regarding the role of financial compensation on symptom reporting have been expressed for many years (49, 53–56). Most researchers suggest that the etiology is due to the biological effects of the injury, psychological factors, psychosocial factors (broadly defined), chronic pain, or a combination of factors (9–11, 14, 39, 57–60). Ruff and colleagues (8, 48, 61) have stressed a multidimensional cumulative stressor conceptualization of the persistent post-concussive disorder. Essentially, setbacks in several aspects of a person’s life (physical, emotional, cognitive, psychosocial, vocational, financial, and recreational) serve as cumulative stressors that interact with personality and premorbid physical and mental health factors, resulting in the disorder. This model stresses the complexity of the etiology and factors that might maintain the symptoms chronically. The model, as written, does not require “brain damage” as a pre-requisite for diagnosis. In addition to cumulative stressors, Wood (13) has described numerous factors that can mimic, reinforce, or perpetuate post-concussion or post-concussion-like symptom reporting.

The ICD-10 criteria explicitly recognize that the cause of the person’s symptoms is not always clear. It has been documented repeatedly by researchers that the

symptoms that comprise the diagnostic criteria are non-specific and they occur frequently in healthy adults and in a variety of patient groups who have not suffered an MTBI (38, 62–77). Examples of the prevalence of these diagnostic criteria in healthy adults, patients with depression, and patients with fibromyalgia are provided in the next section.

### **Nonspecificity of ICD-10 & DSM-IV Diagnostic Criteria**

In this section we provide information regarding the prevalence of the ICD-10 and DSM-IV diagnostic criteria in healthy adults and in patients with depression or fibromyalgia. These data illustrate (a) the nonspecificity of these criteria, and (b) how easy it is to misdiagnose a person with a post-concussive disorder. A post-concussion questionnaire, patterned after the ICD-10 criteria, was developed in the late 1990s and has been used in several studies (73, 78, 79).

The British Columbia Post-concussion Symptom Inventory (BC-PSI; see Appendix A & B) is a 16-item measure designed to assess the presence and severity of post-concussion symptoms (73, 78, 79). The test was based on ICD-10 (40) criteria for Post-concussional Syndrome, and requires the test taker to rate the frequency and intensity of 13 symptoms (i.e., headaches, dizziness or light-headedness, nausea or feeling sick, fatigue, sensitivity to noises, irritability, sadness, nervousness or tension, temper problems, poor concentration, memory problems, reading difficulty, and sleep disturbance), and the effect of three life problems on daily living (i.e., greater present versus past effects of alcohol consumption, worrying and dwelling on symptoms, and self-perception of brain damage).

Normative data for the BC-PSI are available for 158 healthy, community-dwelling, adults from the greater Vancouver metropolitan area. All subjects were working or going to school, and none had a current mental health problem. All were screened for depression and scored below 17 on the Beck Depression Inventory-Second Edition. As seen in Tables 23-2 and 23-3, most healthy adults endorse some symptoms. Approximately 32% of this sample obtained a total score of zero. However, 15% obtained a score of 10 or higher. Scores from 10–14 are considered unusually high and score above 15 are considered extremely high for healthy adults.

The BC-PSI has also been given to large samples of patients with depression or fibromyalgia. The patients with depression were referred by their psychiatrist or family physician (N = 64). All subjects were administered the Structured Clinical Interview for DSM-IV (SCID-I). The SCID-I is a semi-structured clinical interview used to establish DSM-IV Axis I diagnoses. The version of the SCID-I used in this study was the nonpatient research

**TABLE 23-2**  
**Frequencies, Percentages, and Cumulative Percentages of Total Scores in Healthy Adults: British Columbia Post-concussion Symptom Inventory**

TOTAL SCORE	FREQUENCY	PERCENT	CUMULATIVE PERCENT
0	50	31.6	31.6
1	20	12.7	44.3
2	9	5.7	50.0
3	12	7.6	57.6
4	16	10.1	67.7
5	7	4.4	72.2
6	5	3.2	75.3
7	5	3.2	78.5
8	4	2.5	81.0
9	6	3.8	84.8
10	1	0.6	85.4
11	4	2.5	88.0
12	8	5.1	93.0
13	1	0.6	93.7
14	1	0.6	94.3
15	3	1.9	96.2
16	0	0.0	96.2
17	2	1.3	97.5
18	1	0.6	98.1
19	0	0.0	98.1
20	1	0.6	98.7
21	0	0.0	98.7
22	0	0.0	98.7
23	0	0.0	98.7
24	0	0.0	98.7
25	0	0.0	98.7
26	0	0.0	98.7
27	0	0.0	98.7
28	0	0.0	98.7
29	1	0.6	99.4
30	0	0.0	99.4
31	0	0.0	99.4
32	1	0.6	100.0

N = 158.

version 2.0, August 1998 revision (80). All patients had a SCID diagnosis of major depressive disorder (92%), dysthymic disorder (5%), or depressive disorder NOS (3%). The patients with fibromyalgia (N = 54) were recruited from two rheumatology practices and one outpatient hospital program. All patients were examined by a rheumatologist and were included in the study only if they met the American College of Rheumatology criteria for the syndrome (81). On average, the participants had 13.8 trigger points (SD = 2.1, Range = 11–18), and less than one control point (Range = 0–3).

As seen in Table 23-4, mild levels of symptom endorsement occur in a minority of healthy adults and a

**TABLE 23-3**  
**Interpreting Total Scores in Healthy Adults: British Columbia Post-Concussion Symptom Inventory**

TOTAL RAW SCORE	PERCENTILE RANKS	CLASSIFICATION
0	0 – 32%	Low
1 – 9	33 – 85%	Normal
10 – 14	86 – 95%	Unusually high
15+	96 – 100%	Extremely high

The community volunteers were from the Greater Vancouver area (N = 158). All were working or going to school, and none had current mental health problems. The sample was 41% male and 59% female. Their average age was 35.7 years (SD = 16.3). Their average education was 14.8 years (SD = 2.5). They should be considered a high functioning, well-educated sample of healthy adults. The internal consistency reliability (Cronbach's Alpha) for the items comprising the total score is  $r = .82$ .

majority of patients with depression or fibromyalgia. Headaches were reported by nearly 20% of healthy adults, 59% of patients with depression, and 72% of patients with fibromyalgia. Noise sensitivity was reported by 11% of healthy adults, 50% of patients with depression, and approximately 69% of patients with fibromyalgia. The ICD-10 diagnostic criteria also identify reduced tolerance to alcohol, fear of brain damage, and a pre-occupation with symptoms and problems as characterizing the post-concussive disorder. The percentages of patients that endorsed these problems were as follows: (a) reduced tolerance for alcohol (depression = 39% and FM = 35%), (b) concern about having brain damage (depression = 28% and FM = 33%), and (c) worrying about or dwelling on their symptoms and problems (depression = 75%, FM = 85%).

Symptom endorsement for each group can be compared to the DSM-IV and ICD-10 diagnostic criteria. Six of the eight DSM-IV Category C symptoms are represented on the BC-PSI. For the depressed patients, the majority of subjects (85.9%) endorsed three or more DSM-IV Category C symptoms. Over half of the sample (53.1%) endorsed three or more of these symptoms at a clinically significant level (moderate-to-severe). Depressed patients' symptom endorsement also was compared to diagnostic criteria from the ICD-10. All diagnostic criteria from the ICD-10 are represented on the scale. These criteria are grouped into six categories. The specific rates of endorsement for the six mildly endorsed and moderately-severely endorsed symptom categories for the ICD-10 were as follows: (1) headaches, dizziness, general malaise and excessive fatigue, or noise intolerance = 92.2% and 65.6%; (2) irritability, emotional liability, depression, or anxiety = 87.5% and 68.8%; (3) subjective complaints of concentration or memory difficulty = 78.1% and 54.7%; (4) insomnia = 78.1% and 53.1%; (5) reduced

**TABLE 23-4**  
**Percentages of Subjects Endorsing Symptoms at a Mild or Moderate-Severe Level (British Columbia Post-concussion Symptom Inventory.)**

ITEMS	HEALTHY COMMUNITY VOLUNTEERS		PATIENTS WITH DEPRESSION		PATIENTS WITH FIBROMYALGIA	
	MILD	MODERATE-SEVERE	MILD	MODERATE-SEVERE	MILD	MODERATE-SEVERE
Headaches	19.6	3.2	59.4	28.1	72.2	37.0
Dizziness/light-headed	11.4	1.3	31.2	10.9	37.0	7.4
Nausea/feeling sick	13.3	0.0	40.6	10.9	35.2	18.5
Fatigue	27.8	5.1	85.6	57.8	96.3	79.6
Extra sensitive to noises	11.4	1.3	50.0	18.8	68.5	44.4
Irritable	21.5	5.1	76.6	35.9	53.7	25.9
Sadness	18.4	1.3	76.6	56.3	55.6	33.3
Nervous or tense	16.5	1.3	65.6	35.9	59.3	33.3
Temper problems	15.8	5.1	37.5	15.6	27.8	7.4
Poor concentration	16.5	3.2	78.1	46.9	75.9	44.4
Memory problems	13.3	3.8	70.3	42.2	74.1	44.4
Difficulty reading	8.2	1.9	40.6	23.4	48.1	24.1
Poor sleep	22.8	5.1	78.1	53.1	87.0	59.3

Healthy adults (N = 158), patients with depression (N = 64), and patients with fibromyalgia (N = 54). Patients with depression were diagnosed by their family physician or psychiatrist, and their diagnosis was confirmed using the SCID-I. Their average age was 41.1 years (SD = 12.5), and their average education was 14.6 years (SD = 3.2). Approximately 71% of the sample was female. The patients with fibromyalgia were mostly women (94%). Their average age was 51.4 years (SD = 12.8, Range = 17 – 75). Their average education was 13.5 years (SD = 2.4, Range = 7 – 20)

tolerance to alcohol = 35.9% and 12.5%; and (6) pre-occupation with these symptoms and fear of permanent brain damage = 76.6% and 26.6%. The majority of the sample (89.1%) endorsed three or more ICD-10 Category C symptoms, with 57.8% endorsing these symptom categories at a clinically significant level.

The patients with fibromyalgia had similar results. The majority of subjects (81.5%) endorsed three or more DSM-IV Category C symptoms. Half of the sample (50.0%) endorsed three or more of these symptoms at a clinically significant level (moderate-to-severe). Their specific rates of endorsement for the six mildly endorsed and moderately-severely endorsed symptom categories for the ICD-10 were as follows: (1) headaches, dizziness, general malaise and excessive fatigue, or noise intolerance = 96.3% and 83.3%; (2) irritability, emotional lability, depression, or anxiety = 81.5% and 50.0%; (3) subjective complaints of concentration or memory difficulty = 77.8% and 53.7%; (4) insomnia = 87.0% and 59.3%; (5) reduced tolerance to alcohol = 35.8% and 33.3%; and (6) preoccupation with these symptoms and fear of permanent brain damage = 87.0% and 63.0%. The majority of the sample (94.3%) endorsed three or more ICD-10 Category C symptoms, with 66% endorsing these symptom categories at a clinically significant level.

What is clear from the data presented in this section is that (a) the diagnostic criteria for the post-concussive disorder are non-specific, and (b) patients with fibromyalgia who report problems with depression, chronic pain, or both are very likely to be diagnosed (or misdiagnosed) with the disorder. In fact, 9 out of 10 patients with depression or fibromyalgia report a symptom constellation that can meet criteria for a post-concussive disorder (in the absence of a traumatic injury to their head or brain). The rates at which the patients with depression and the patients with fibromyalgia met diagnostic criteria for the two classification systems were very similar because only the symptom criteria were applied. The additional DSM-IV criteria for measured neurocognitive impairment and impairment in real-world functioning were not applied. What is interesting, of course, is that when patients are followed prospectively out of the hospital and assessed at three months post-injury, a minority meet DSM-IV criteria (11–17%) and over half meet ICD-10 criteria (54–64%) (46, 47). However, as illustrated with this section of the chapter, if a person has depression (and no head or brain injury), he or she is 90% likely to meet ICD-10 criteria (if the head injury criterion is waived). The remainder of the chapter addresses the complexities of differential diagnoses.

## DIFFERENTIAL DIAGNOSES AND CO-MORBIDITIES

There are many possible differential diagnoses, comorbidities, and social-psychological factors that may *cause or maintain* the myriad of symptoms and problems reported by patients long after experiencing a mild injury to their head, brain, or both. These differential diagnoses or co-morbidities might be largely unrelated to the original MTBI. In practice, it is oftentimes difficult to disentangle the many factors that can be responsible for the symptoms following a remote MTBI or a craniocervical trauma with an MTBI. This is because the more chronic symptoms that are believed to be associated directly or indirectly to the remote injury are common in healthy subjects (62, 72–77), in patients with no history of brain injury, such as outpatients seen for psychological treatment (63) or minor medical problems (64), personal injury claimants (64, 65), patients with post-traumatic stress disorder (66), patients with orthopedic injuries (38), individuals with chronic pain (67–70), and patients with whiplash (71). Thus, the differential diagnosis of the persistent post-concussive disorder is very challenging. The most commonly encountered clinical conditions that might lead to a diagnosis of “post-concussive disorder” are traumatic cervical injuries due to whiplash-associated disorders; post-traumatic chronic pain, particularly headache (cephalgia) and neck pain (cervicalgia); depression; and the anxiety spectrum disorders (including post-traumatic stress disorder). Each of these conditions might co-occur with an MTBI or they might occur independently from an MTBI. If they co-occur, the challenge is trying to determine if the person recovered from the MTBI and the ongoing symptoms and problems reported are more likely to relate to one of the co-morbid conditions. These conditions will be reviewed next.

### Cervical Injuries and Whiplash-Associated Disorders

Cervical spine injuries are common, particularly following rear-end motor vehicle accidents (82). Most patients recover from these injuries in a few weeks. However, there are others who have longer-term problems related to numerous potential secondary complications. The diagnostic and treatment challenges are mainly relevant to this chronically-symptomatic group.

It is generally agreed that whiplash injury typically involves a flexion-extension movement, but torsional-rotational movement may also play a role. The presumed cause of the acute injury is mechanical strain with or without contusion of ligaments and muscles supporting the cervical spine. Safety belts appear to actually increase the risk for cervical injury and, to a lesser extent, thoracic vertebral fractures (83). Because most cervical acceleration/

deceleration injuries are not exclusively in the sagittal plane, the pathomechanics can be complicated and this has important implications for what part of the neck might be damaged as a result of rotational injury. Structures that become more susceptible to injury when there is cervical rotation include the facet (zygapophyseal) joint capsules, alar ligament complex, and intervertebral discs (84). The forces involved in cervical injury include extension, flexion, lateral flexion, and shear. Shear forces typically are horizontal in nature. Cervical symptoms may be caused and maintained as a result of injury to multiple structures within the neck including intervertebral discs, muscles, ligaments, the atlantoaxial complex, cervical vertebra, zygapophyseal (facet) joints, and neurovascular structures (85). Imaging methods, particularly conventional radiography, do not visualize many of these types of lesions very well.

The most common acute symptoms following whiplash are neck pain, headache, and limitation in neck range of motion (82, 86, 87). Many other symptoms have been associated with this type of injury, including visual disturbances, dizziness, auditory disturbances, balance disorders, and cognitive dysfunction (85, 88).

Visual disturbances have been associated with whiplash and might be subjectively reported as “blurriness”. Most commonly, this subjective impairment is associated with findings of decreased accommodative and convergence function (89, 90). Other problems, such as disturbances in saccadic eye movement, have also been reported (91).

Cervicogenic vertigo or dizziness is a complaint that often accompanies cervical whiplash injury and may be related to (a) problems with the afferent input from positional proprioceptors in the cervical and lumbar regions (92, 93), (b) over-excitation of the cervical sympathetic nerves (94), (c) compromise of vertebral artery blood flow (95, 96), and/or (d) cervical/lumbar hypertonicity (94). Non-cervicogenic causes of vertigo or dizziness include perilymphatic fistulas<sup>1</sup>, post-traumatic endolymphatic hydrops<sup>2</sup> (e.g., Meniere’s disease), and benign paroxysmal positional vertigo<sup>3</sup> (97–99). Some patients report general feelings of whooziness, giddiness, and/or imbalance. Stapley and colleagues hypothesized that this phenomena occurs as a result of neck muscle fatigue and associated increases in postural body sway (100). Balance disorders

<sup>1</sup> An abnormal communication between the fluid-filled perilymphatic space of the inner ear and the air-filled middle ear cavity.

<sup>2</sup> Increased hydraulic pressure within the inner ear’s endolymphatic system that can cause hearing loss, episodic vertigo, tinnitus, and pressure sensation.

<sup>3</sup> Benign paroxysmal positional vertigo can occur following head trauma and might relate to a collection of debris in the inner ear. Symptoms include dizziness or vertigo, light-headedness, imbalance, and nausea.

following whiplash are believed to be associated with (a) altered vestibular and/or proprioceptive input (101), (b) neck muscle fatigue (102), (c) joint position error (103), and/or (d) abnormal cervical afferent input (104).

Auditory symptoms, such as tinnitus, hyperacusis<sup>4</sup>, and hearing loss (105, 106), may also occur following whiplash. There is controversy regarding the etiology of neuro-otological impairments of these types following cervical whiplash, but they clearly can occur in the absence of acquired brain injury. The cause of tinnitus has not been determined definitively, but it is possible that following whiplash cranio-cervical somatic dysfunction may modulate dorsal cochlear nucleus activity (107), and/or aberrant nociceptive input to the brainstem from upper cervical (e.g., atlas) and associated cervical myofascial dysfunction (108) may be the underlying cause(s). Temporomandibular joint dysfunction also might underlie tinnitus in some patients (109).

Neurocognitive complaints also are common following whiplash (110), and a substantial minority of patients remain symptomatic at one year post-injury (111, 112). These problems should be conceptualized as either perceived, self-reported symptoms or measured problems on neuropsychological tests. In a meta-analytic review of the literature, Kessels and colleagues (113) concluded that cognitive functioning, as measured by neuropsychological tests, can be adversely affected following whiplash. Not all studies, of course, report neuropsychological changes associated with whiplash injury (e.g., 114). The cause of cognitive complaints or measured cognitive decrements in a subset of patients with whiplash is unknown; researchers suggest they might be related to damage to the brain (110), somatization (114), distraction due to pain (115), or a combination of factors.

There are multiple potential causes of chronic pain following whiplash. Possible etiologies, singly or in combination, include myofascial dysfunction of the paracervical (anterior and posterior) and upper shoulder girdle musculature, C2-C3 facet joint pain, neuralgia of the greater and/or lesser occipital nerve, internal derangement of the temporo-mandibular joint, basilar artery migraine, and/or cervico-thoracic somatic dysfunction (116). Facial, neck, and shoulder dysesthesias (e.g., burning, pins and needles, itching sensation) can arise from the upper cranial nerves and their superficial branches (greater auricular nerve, superficial cervical nerve, and supraclavicular nerve), and the descending tract of the trigeminal nerve and/or its associated fibers (i.e., fibers 5, 7, 9, and 10). Knibestol and colleagues reported that some patients with whiplash have facial sensory changes in vibratory and temperature perception that might be related to damage to the central trigeminal system in the upper spinal cord segments and pontomedullary levels of the brainstem (117). Herren-Gerber

and colleagues reported that there is modulation of central hypersensitivity by nociceptive input following whiplash injury and that different mechanisms likely underlie hypersensitivity to pain (hyperalgesia) localized to areas around the pain site versus distant body areas (118). Chronic cervical facet joint pain can occur following whiplash. Dwyer and colleagues “mapped” characteristic patterns of cervical zygapophyseal joint pain in normal volunteers; this mapping may be useful for constructing pain charts (119).

The best initial treatment for cervicogenic pain is exercise and manual therapy. In more intractable cases, where facet involvement is suspected, interventional pain management through the use of local blocks and/or neuromodulation procedures is recommended (120, 121).

### Cranial Trauma

Head injury can, of course, result in damage to the skull or its adjoining parts (i.e., the cranium or cranial adnexal structures). This damage might underlie some of the symptoms and problems reported by patients acutely and post-acutely without necessarily having concomitant brain injury (98).

Skull fractures are relatively uncommon in patients who sustain mild traumatic brain injuries. When they occur, they may be closed or compound and depressed or non-depressed. Basilar skull fractures, as opposed to linear skull fractures of the cranial vault, often have important clinical implications. If the dura mater is torn, the chance of a cerebrospinal fluid fistula is increased. A dural tear or basilar skull fracture will increase the patient's risk of meningitis. Cerebrospinal fluid leaks may occur through the nose (rhinorrhea) or ears (otorrhea) and may be missed in the acute setting. Approximately 4% of mild head injury patients may have an unsuspected temporal skull fracture (122).

Hearing loss can arise from damage to cranial adnexal structures. Longitudinal fractures are more commonly associated with conductive hearing loss due to either ossicular chain disruption or traumatic tympanic membrane tear and blood in the middle ear. Transverse temporal skull fractures often will be associated with either mixed or profound sensorineural hearing loss, hemotympanum, dizziness, and/or facial nerve injuries (123, 124). The conductive hearing loss associated with hemotympanum is typically temporary and resolves as the blood is re-absorbed. Progressive hearing loss following trauma should prompt further assessment for either perilymphatic fistula or endolymphatic hydrops (125). The most common type of ossicular dislocation associated with temporal skull fractures is the separation of the incudostapedial joint, with or without dislocation of the body of the incus from the articulation with the malleus head. Surgical correction can restore hearing.

<sup>4</sup> Hypersensitivity to sound.

Complaints of “dizziness” following head trauma and/or mild traumatic brain injury are extremely common. If these problems persist beyond the acute stage of recovery, thorough clinical evaluation is important. Neurodiagnostic evaluation of the dizzy patient might include: audiologic testing, a platform fistula test, electronystagmography, and/or posturography (99, 126). Labyrinthine concussion can result in transient auditory and vestibular symptoms without associated skull fracture. Sudden deafness following a blow to the cranium may be partially or completely reversible. Benign paroxysmal positional vertigo is the most common neuro-otologic problem following head trauma. Most patients demonstrate a paroxysmal positional nystagmus with rapid changes in position (127). Although, benign paroxysmal positional vertigo may have periodic exacerbations even after the symptoms have subsided, this is the exception rather than the rule. Vestibular suppressant medications may be used, but generally these agents should only be considered if symptoms are severe enough to dramatically compromise functional activities such as frequent falls or significant nausea and/or vomiting. Vestibular exercises may also be prescribed to hasten neurologic and functional recovery via several proposed physiologic mechanisms including central sensory substitution, rebalancing tonic activity, and physiologic habituation (128–132). Clinical researchers suggest that a three-pronged approach should be utilized as part of an organized vestibular rehabilitation program: (a) habituation exercises, (b) postural control exercises, and (c) general conditioning activities (133). Surgery may be considered as a last resort for intractable benign paroxysmal positional vertigo; it has been reported to be successful in more than 90% of cases (134).

The clinician should always consider the possibility of a post-traumatic endolymphatic hydrops (Meniere’s syndrome) after cranial trauma when there is ipsilateral low-frequency hearing loss, tinnitus, and a sensation of fullness in the ear. Treatment of post-traumatic Meniere’s disease may include vestibular suppressants if patients are symptomatic to the point that daily function is significantly adversely affected. Head movements and rapid changes in head position should be avoided. In the remission phase, Meniere’s disease may be treated with medications including vestibular suppressants and/or diuretics as well as steroids, low pressure pulse generators (Meniett device), and surgical procedures (both destructive and non-destructive; 135, 136–138).

Post-traumatic perilymphatic fistula can occur following trauma as a result of rupture of the oval and less commonly the round window with subsequent communication between the inner ear and middle ear resulting in inappropriate stimulation of labyrinthine receptors (139). Unfortunately, there is no pathognomonic or characteristic electronystagmographic sign for the condition. Symptoms can include vertigo, fluctuating hearing loss

(usually a late complication), tinnitus, chronic low grade nausea, endolymphatic hydrops, abnormal cervical muscle tone (myodystonia), and persistent or exertional headache (140). Patients quite frequently complain of aural fullness (141). Patients will often complain of non-specific imbalance problems worsened by sudden turning, as well as disequilibrium with perceptually-complex external stimuli such as patterns and wide-field motion evidenced with escalator rides, revolving doors, and crowds (141, 142). The sensation while ambulating has been described as “walking on pillows” (135). The aforementioned experiences sometimes promote a mild agoraphobia. Although there is no definitive bedside clinical test for post-traumatic perilymphatic fistula, application of pressure to the tympanic membrane with a pneumatic otoscope (Hennebert’s fistula test) or application of pressure over the tragus might produce worsening of vertigo or nystagmus. Both the aforementioned tests are suggestive but not diagnostic for a perilymphatic fistula. Some investigators believe that caloric hypoexcitability or unexcitability associated with even partial conservation of cochlear function is a very good indicator of the condition (143). Black, Lilly, and Nashner (144) described the platform fistula test utilizing posturography as a means of objectively diagnosing this clinical condition. The ability of posturographic testing to delineate perilymphatic fistulas has been questioned by one of the authors (NDZ) as well as others (145). However, further research is definitely indicated to clarify the role of this diagnostic modality. Early treatment measures include bedrest, head elevation, and avoidance of straining (135). The duration of bedrest is somewhat controversial although many clinicians advocate 5 to 10 days given the functional and physiologic implications of prolonged immobilization. Perilymphatic fistulas usually heal spontaneously. Exploratory tympanotomy is necessary to definitively establish the diagnosis, but is generally *not* recommended unless symptoms last longer than a month or if there is a progressive hearing loss. Chronic perilymphatic fistulas can be addressed surgically by “patching” the leaking oval/round window utilizing temporal aponeurosis or stapledectomy with interposition (146). Recent work has shown that the presence of beta-2 transferrin may serve as a marker for perilymphatic fistula-related leaks (147, 148). Surgical treatment generally aids in control of vertigo much more so than the restoration of hearing (141, 143).

Tinnitus can occur following head trauma. It is important to note that tinnitus is a symptom not a disease entity, the etiology of which must be defined before it can be effectively treated. Audiologic battery testing is indicated in all post-head injury patients with complaints of tinnitus. Hearing aids, cochlear implants, tinnitus maskers, and hearing instruments have been used to decrease the subjective symptoms associated with this disorder. The protocol that is clearly the most well

accepted is the Jastreboff tinnitus retraining program<sup>5</sup> (149). No drug has been FDA approved for treating tinnitus and current choices are at best controversial and poorly studied (150). Antidepressant medications, biofeedback, hypnosis, avoidance of stimulants including caffeine, and proper sleep hygiene have also been recommended because tinnitus can be exacerbated by stress and anxiety (151).

Olfactory and gustatory problems also can occur following injury to the cranium and/or brain. There are several million olfactory neurons located in the olfactory epithelium on the wall of the nasal cavity. Each of these neurons extends an axon to the olfactory bulb (on the surface of the brain, along the orbital-medial surface of the frontal lobe). The bulb neurons extend axons, via the olfactory tracts, to make contact with neurons located in the olfactory cortex. The primary olfactory cortex is located near the anteromedial part of the uncus on each side. Because the olfactory tract is attached to the outer aspect of the hemisphere, the impact of the skull's jagged interior<sup>6</sup> upon the uncus could damage the primary olfactory cortex or the terminal portion of the olfactory nerve or both. Costanzo and Zasler (153) listed the known and presumed mechanisms underlying olfactory impairment following head trauma or TBI as follows: (1) traumatic damage to the nasal epithelium; (2) shearing of the olfactory fila, arising from the nasal epithelium, prior to entering the olfactory bulbs, as a presumed consequence of movement of the brain relative to, and/or fracture of, the cribriform plate; and (3) contusions or edema effecting the olfactory bulb or the lateral or medial olfactory tracts. All of these mechanisms could cause impairment in the ability to detect odors. Isolated gustatory dysfunction is uncommon. Typically, peripheral injury involves the facial nerve (CN VII) because it is more prone to injury than the glossopharyngeal (CN IX) and vagus (CN X) nerves which are also involved in mediation of taste (153). Timely neuromedical and rehabilitative interventions (154) including comprehensive objective quantification of deficits through established "Chemosensory Clinics" can be helpful.

Visual problems can occur at a peripheral level and be unrelated to a brain injury. These deficits can be due

<sup>5</sup> The authors know specialists in neuro-otology that strongly prefer to not take patients into a tinnitus retraining program while they are involved in litigation, given limited resources and less "subjective improvement" in patients involved in stressful, adversarial, protracted litigation.

<sup>6</sup> The upper border of the sphenoid bone is sharply angulated, like the edge of a shelf. In the center of the skull base, the sphenoid wings or ridges terminate in two bony projections called the anterior clinoid processes. They are adjacent and immediately anterior to the uncus on both sides and point posteriorly towards the foramen magnum. Therefore, with a violent forward movement of the brain relative to the skull, the anterior clinoid processes could produce contusions in the region of the uncus (152).

to disorders of the vitreous, both prefoveal and foveal, commonly associated with traction on the retina with resultant subjective symptoms of floating spots (so-called "floaters"; 155, 156). Retinal injury, including detachment, tear, and hemorrhage (157, 158), also causes visual symptoms. Approximately 20% of patients evaluated with mid-facial trauma were noted in one study to have accommodative and/or convergence insufficiency (159). A cursory assessment of the optic disc by the physician will obviously miss the types of subtle lesions responsible for many post-traumatic visual symptoms. It is therefore important to refer patients with visual complaints for appropriate diagnostic assessment as well as functionally oriented treatment. Professionals that may assist in these aforementioned areas include ophthalmology, neuro-ophthalmology, and neuro-optometry (See chapter in this text by Padula and colleagues).

Headache and neck pain are the most common physical complaints following concussion (mild brain injury) (See chapters in this text by Zasler, Martelli, et al. and Martelli, Zasler, et al. on Pain Management). Headaches, of course, are common in the general population as well (160, 161). Pre-existing headaches, post-traumatic headaches, or both might largely underlie a diverse set of symptoms and problems in people who have sustained an MTBI (as well as patients with whiplash-related problems or cranial-trauma related problems). Patients with problematic headaches, such as migraine or tension, often have comorbid depression (162–165). Elevated levels of psychological distress (i.e., symptoms of anxiety, depression, or both), that may or may not break threshold for diagnosing a psychiatric condition, have been reported in numerous studies involving patients with headache conditions (166–171).

When a patient presents with headaches long after an MTBI, it is difficult to determine whether (a) the original injury is the underlying cause of the headaches, and (b) to what extent other factors have caused, or are maintaining, the headaches. It is estimated that 4–5% of adults experience chronic daily headaches (172, 173). Medication overuse (i.e., drug rebound headache) is the most treatable cause of refractory headaches (174–179). Medication overuse might result from patients' attempt to treat their headaches or other bodily pain. Febrile or viral illnesses, general surgery, or a stressful life event appear to be the most common events that precede new daily persistent headaches (180).

When a person is involved in litigation, headaches typically are attributed to the tort (i.e., injury being litigated). Of course, headaches are common in daily life and people who are not involved in litigation attribute a variety of factors to the underlying cause of their headaches. Boardman and colleagues (181) conducted a large-scale survey study of adults in Great Britain. In this sample of 1, 871 adults who suffered from headaches in the past



3 months, factors *perceived* (i.e., self-reported) to be related to their headaches were as follows: stress (71%), tiredness (65%), menstrual cycle (55%), having too much work to do (41%), drinking alcohol (33%), sleeping too long (21%), and not eating regularly (20%). The respondents also completed several psychological tests (e.g., measuring depression and anxiety) and questionnaires (measuring pain, disability, sleep problems, and alcohol and caffeine consumption). Headache occurrence was most strongly associated with anxiety and sleep problems.

### Chronic Pain

Patients with chronic pain often complain of physical, cognitive, and psychological symptoms that closely resemble post-concussion-like symptoms (e.g., 68, 70, 114, 182–189). If chronic pain does not co-occur in patients who are slow to recover following an MTBI, then the similarity between chronic pain symptoms and post-concussion symptoms is not problematic. However, patients who sustain MTBIs in falls or motor vehicle accidents frequently have a comorbid chronic pain problem. Uomoto and Esselman (190) reported that 95% of patients with MTBI's reported the presence of at least one chronic pain symptom 24 months post-injury (e.g., headaches, neck/shoulder pain, or back pain). Thus, because chronic pain often accompanies MTBI, attributing post-concussion symptoms to brain injury in patients with comorbid pain is problematic.

McCracken and Iverson (185) reported that 54% of chronic pain patients from a university pain management center endorsed at least one subjective cognitive complaint (e.g., forgetfulness, minor accidents, difficulty finishing tasks, difficulty with attention). Roth et al. (187) found that 62% of chronic pain patients from a university hospital pain management program reported experiencing at least one subjective cognitive complaint as being a moderate to severe problem, and 28% of the patients endorsed 5 of 5 cognitive complaints as being a moderate to severe problem (i.e., trouble remembering, having to recheck things, difficulty making decisions, mind going blank, and trouble concentrating). Jamison, Sbrocco, and Parris (184) found that 54.5% of chronic pain patients from a university medical pain control center reported having moderate to extreme problems with both memory and concentration.

In a study comparing post-concussion-like symptoms to DSM-IV criteria for Post-concussional Disorder, Iverson and McCracken (68) examined 170 non-litigating, chronic pain patients with no history of head injury. On self-report inventories, 42% of these patients reported at least one cognitive complaint that had an impact on their health (i.e., attention, concentration, or memory). A large percentage (80.6%) of these patients endorsed three or

more of the symptoms from Category C of the Post-concussional Disorder criteria in the DSM-IV (41). The percentage of these patients who would meet self report criteria for a Post-concussional Disorder was calculated by determining the number of patients who reported cognitive problems and three or more symptoms from Category C. Based on self report alone, 39% of the chronic pain patients met criteria for a Post-concussional Disorder (except, of course, they had no history of head injury).

Gasquoin (67) compared post-concussion-like symptom reporting in a small sample of 10 patients with MTBIs and 18 patients with chronic back pain. No differences between the MTBI group and chronic back pain group were found on any PCS symptoms, even on symptoms that were typically "head injury related" (e.g., headache, dizziness, recent memory, concentration). Smith-Seemiller and colleagues compared symptom reporting on the Rivermead Post-concussion Questionnaire in 32 patients with chronic complaints following an MTBI and 63 chronic pain patients. More than 80% of both groups met DSM-IV self-report symptom criteria for a Post-concussional Disorder. No differences between groups were found on the total post-concussion symptoms. However, on the subscales of the Rivermead Post-concussion Questionnaire, the MTBI patients endorsed more cognitive symptoms and fewer emotional symptoms compared to the chronic pain patients. There were no differences between groups on the somatic symptoms of the Rivermead. These authors cautioned, however, that there was a high base rate of patients undergoing litigation in the chronic pain sample that may have biased symptom reporting in this group (70).

Some researchers have suggested that the reporting of cognitive complaints in chronic pain patients may be associated with depression, anxiety, and fatigue (e.g., 185–187). Similarly, these complaints may be influenced by factors including the pain experience itself, comorbid psychiatric disorders, medication side effects, iatrogenic factors, and possible malingering. However, the influence of these factors is poorly understood. Given that (a) chronic pain conditions frequently accompany MTBI many months post-injury (190), (b) patients with chronic pain report identical symptoms as those attributed to a post-concussive disorder (e.g., 68, 70), (c) depression frequently co-occurs with chronic pain (191–195), and (d) patients with depression report very similar symptoms as those attributed to a post-concussive disorder (cf. the DSM-IV diagnostic criteria and associated features and Iverson (79)), it is not surprising that a person with chronic pain can be easily misdiagnosed as having a persistent post-concussive disorder, or chronic pain might be the predominant underlying cause of the disorder (See chapters in this text by Zasler, Martelli, et al. and Martelli, Zasler, et al. on Pain Management).

### Depression, Anxiety, Stress, and Somatic Preoccupation

Depression is common following traumatic brain injuries of all severities (196, 197). Depression is also common in patients with chronic pain (191, 194), and it is associated with increased disability in these patients (193, 198). Depression is also common in trauma patients (199), and patients with chronic headaches (165, 200–202), post-traumatic stress disorder (66, 203–205), or substance abuse problems (206–210). Of course, depression is one of the most common mental health problems in the world, and people who suffer a single episode of major depression are at greatly increased risk for a future episode, with estimates of recurrence ranging from 50% to 80% (211–215). People who have had two or more episodes of depression are at extremely high risk for a future episode (43, page 372, 213, 216–218). Therefore, the underlying cause of depression, in any given person at any given time, can be very difficult, if not impossible, to determine. Depression represents the most challenging differential diagnosis for the post-concussive disorder (of course, depression might be the predominant etiology of the disorder for some patients). Many of the specific symptoms of depression, and other problems associated with this condition, are similar to the post-concussive disorder. The diagnostic criteria for major depression include the following symptoms: (a) diminished ability to think or concentrate, (b) indecisiveness, (c) fatigue or loss of energy, and (d) sleep problems (DSM-IV; 41; p. 327). In addition, major depression often is associated with irritability, excessive worry over one's health, and headaches (41; p. 323). Common lifestyle and psychosocial problems include strained social relationships, marital and family distress, occupational problems, academic problems, and substance abuse (41; p. 323). Therefore, it is extremely difficult to determine if a person's self-reported symptoms are due to depression, a persistent post-concussive disorder, or both because many of the symptoms are nearly identical in these conditions.

Patients with depression are expected to have cognitive complaints. Perceived cognitive impairment is a *cardinal feature* of depression (43). However, the relation between depression and cognitive difficulty goes much further. The co-occurrence of perceived cognitive problems and symptoms of depression has been demonstrated repeatedly in the literature in diverse groups of unselected community-dwelling adults (219–221) and specific clinical groups, such as patients with cancer (222), chronic fatigue syndrome (223), HIV (224, 225), major non-cardiac surgery (226), epilepsy (227, 228), chronic pain (185, 188), and sleep apnea (229). This is a consistent finding across different cultural and ethnic groups, including Chinese (230), French (231), Dutch (232), and African Americans (233). Therefore, broad and diverse research converges to illustrate clearly that the diagnosis

of depression, or a depressive experience that does not meet criteria for a diagnosis, is likely to be accompanied by perceived cognitive problems.

The perceived cognitive problems reported by patients with depression have been illustrated more objectively through neuropsychological studies (234–247). However, there has never been a study showing that the cognitive effects of depression can be reliably differentiated from the cognitive effects of an MTBI. The problem for clinicians and researchers is that a person with depression is virtually guaranteed to meet diagnostic criteria for a post-concussive disorder, regardless of whether that person (a) has ever injured his brain, or (b) the past injury to his brain is causally-related to his current symptoms.

Another challenging differential diagnoses for the post-concussive disorder is Post-Traumatic Stress Disorder (PTSD). Patients with PTSD often report the same symptoms as patients who have sustained MTBIs. For example, in a sample of 128 patients with PTSD, 89% reported irritability, 56% reported memory problems, 92% reported concentration problems, and 90% reported difficulty sleeping (66). Therefore, it is easy to misdiagnose PTSD as a post-concussive disorder, and vice versa.

A controversial and confusing issue is whether a person who sustains a traumatic brain injury involving amnesia for the event can develop PTSD. There are data to support the position that TBI and PTSD typically are mutually exclusive (248–250), although researchers have put forward a compelling rationale for how, under certain circumstances, PTSD could emerge in a patient with a brain injury in the presence of amnesia (251, 252). The conceptual question at the heart of the debate is whether a person with no memory for a traumatic event can develop PTSD as a result of that traumatic event.

Gil and colleagues prospectively studied 120 accident victims who sustained an MTBI and who were hospitalized for observation immediately after their trauma. They were assessed within the first 24 hours and at one week, three months, and six months. At six months post-injury, 14% met diagnostic criteria for PTSD (notice that this prevalence rate is very similar to the rate of people believed to have the post-concussive disorder at 6–12 months post-injury). The statistical predictors of PTSD at 6 months were (a) PTSD symptoms, depressive symptoms, and anxiety symptoms at one week post-injury, (b) history of psychiatric disorder, and (c) memory for the event. Of the patients with memory for the event, 13/55 (23%) had PTSD at 6 months post-injury, compared to only 4/65 (6%) who did not have memory for the event (253). Therefore, the literature to date suggests quite clearly that having no memory for the event likely protects the individual from developing PTSD.

Therefore, a person who sustains an MTBI who has upsetting and traumatic memories of the accident, assault, or injury, and who has nightmares and sleep disturbance,

might have PTSD, a post-concussive disorder, or both. It is extremely difficult to accurately diagnose both conditions in a patient, and the combination of the two is statistically uncommon. Therefore, it is more parsimonious to diagnose, and treat, the PTSD if it appears to be present and wait to see if the patient has ongoing residual problems that might relate to a brain injury following improvement or remission.

Symptoms of anxiety, stress, and somatic preoccupation also occur frequently in patients who are symptomatic beyond a few weeks post-injury. In a prospective study, Ponsford and colleagues reported that patients who were symptomatic at three months post-injury were likely to have high levels of stress and anxiety (254). As noted in the ICD-10 diagnostic criteria, symptoms following an MTBI “may be accompanied by feelings of depression or anxiety, resulting from some loss of self-esteem and fear of permanent brain damage. Such feelings enhance the original symptoms and a vicious circle results. Some patients become hypochondriacal, embark on a search for diagnosis and cure, and may adopt a permanent sick role” (40; section F07.2). Clinicians working with symptomatic patients are acutely aware that anxiety, and fear of permanent brain damage, can be prominent psychological features. Clinicians should take steps to reduce patients’ subjective distress and guard against behavior that can be iatrogenic.

### IATROGENESIS

An iatrogenic condition is a state of ill health or adverse effect caused by medical treatment, usually due to mistakes made in treatment (255). The word literally means “caused by a doctor” (*iatros* means physician in Greek), though such conditions can be the fault of therapists and/or pharmacists as well. This phenomenon is poorly researched in the field of rehabilitation, neurology, and neuropsychology, and there is no literature per se on the topic as related to MTBI. Nonetheless, it is a well-recognized issue in the field of brain injury rehabilitation.

Professionals involved in rehabilitation have a clinical responsibility to patients with MTBI. To the extent that symptoms are ever iatrogenic, we provide a disservice to patients. To the extent that symptoms are neurologically, emotionally, environmentally, or motivationally based, we have a responsibility to understand and address these issues clinically to the best of our ability (Ref. 256, p. 57).

The tendency for medical, medical-legal, and rehabilitation professionals to diagnose “brain damage” or “diffuse axonal injury” as an explanation for persistent problems following a mild uncomplicated concussion (i.e., a “mild MTBI”) can be iatrogenic. The authors have

seen, on numerous occasions, psychological harm resulting from telling people they have brain damage and they will need to cope and compensate for that damage, when in fact the probability of permanent brain damage was very low and the probability of a “treatable condition”, such as depression, anxiety, sleep disturbance, and cumulative life stress, was high. Remember, if a person has chronic bodily pain, depression, or both, they are virtually guaranteed to meet self-report criteria for a post-concussive disorder regardless of whether they ever sustained a concussion. When a person is misdiagnosed as having presumed permanent brain damage it sends a strong, negative, prognostic message. It also might lead to (a) the person seeking support from brain injury associations, (b) the person receiving rehabilitation services normally designated for patients with moderate to severe brain injuries, and (c) the failure to provide effective treatment for the person’s real underlying problems.

Roger Wood has noted that the early iatrogenic potential of general practitioners and hospital doctors may create insecurity and/or reinforce illness perceptions thereby instigating perceptions of disability and “illness behavior” due to both negative expectancies and the nocebo effect (see below) (13). Certainly, incorrect diagnosis may lead to treatment that is potentially both ineffective and possibly deleterious, physically and/or psychologically, to the patient. Oftentimes, misidentification and mislabeling of patients produces perpetuation of the actual impairment(s) and creates a more recalcitrant condition with a poorer prognosis (257). Parallel to experiences with pain patients, persons with MTBI may experience the negative ramifications of iatrogenesis in the context of over-investigation, particularly with unproven “neurodiagnostic” techniques, inappropriate information and advice, misdiagnosis, over-treatment, and inappropriate medication prescription (the latter which may produce further impairment and/or complications) (257). Iatrogenesis may not only have negative consequences on the patient but also on their family and/or significant other(s).

Physicians and other health care clinicians should be sensitized to the importance of avoiding iatrogenic complications. Some have considered iatrogenesis to be a “violation of moral norms, insufficient professionalism, negligence and indifference” (258). Others might argue that what sometimes appears to be iatrogenic illness may in fact be driven by unethical clinical practice, examiner bias, and/or examiner secondary gain. There are tremendous financial and professional pressures and incentives in the medical-legal setting, and it is widely believed that some experts adopt rather extreme, predictable, and polarized opinions that result in routine labeling of people as having long-term problems due to, presumably, permanent brain damage following a mild concussion. Better guidelines are clearly necessary to aide clinicians evaluating

and treating persons with MTBI to avoid iatrogenesis. Moreover, everyone involved with patients conceptualized as having a post-concussive disorder should be aware of the numerous psychological factors that can cause or maintain the condition. These psychological factors are not only important for understanding the disorder, they represent obvious, typically overlooked, areas for treatment.

### FACTORS RELATING TO THE PERCEPTION AND REPORTING OF SYMPTOMS

A diverse range of psychological factors can influence the perception and reporting of symptoms long after an MTBI. A person's psychological history, emotional response to injury, coping mechanisms, and psychosocial environment (e.g., work and family) are all factors that can influence the perception and reporting of symptoms and problems, as well as impact how the person functions in day-to-day life.

The experience of being ill can, in some ways, be rewarding for the patient. For example, the patient may get special privileges and extra attention from their spouse, family, coworkers, and friends. For many years, these issues have been studied in patients with chronic pain syndromes. Researchers have demonstrated that extra attention, changes in household responsibilities and routines, and the avoidance of undesirable activities all can *increase* patients' reporting of pain and disability. It is reasonable to think that some individuals with persistent symptoms and problems following an MTBI, similar to chronic pain patients, could derive reinforcement for disability behaviors. This is sometimes referred to as a *reinforced behavior pattern*.

The next section provides an overview of the role of personality characteristics and disorders in outcome from MTBI. The following sections relate to important social-psychological factors and influences on the etiology and maintenance of symptom experiencing and reporting in some patients.

#### Personality Characteristics and Disorders

Personality characteristics influence how people respond to illness, injury, or disease. Therefore, these characteristics are likely to be very important for understanding who is at risk for developing a persistent post-concussive disorder, and some of the psychological factors that maintain the disorder. At present, there is limited research available regarding the influence of personality styles as they might apply to the development, exacerbation, and maintenance of symptoms and problems following an MTBI.

As clinicians, it is very common to see a great deal of variation in individual response styles to life stressors

and/or traumatic events. Although most people tend to be remarkably resilient to traumatic life events or injuries, some individuals are emotionally fragile and have relatively catastrophic reactions to seemingly small events. To most of us, it makes perfect intuitive sense that premorbid personality factors would influence individual response styles to life stressors and/or traumatic events.

In psychiatry and psychology, there is considerable interest in the role of personality characteristics in the etiology of mental health problems. This large literature, by extension, is relevant to understanding the post-concussive disorder, and the differential diagnosis of this disorder. Researchers frequently have reported that certain personality characteristics appear to be risk factors for major depression. People with high levels of neuroticism or negative affectivity, low self-esteem, and poor life coping skills are at increased risk for developing depression (259–263). These same personality characteristics, in addition to anger/hostility and narcissism, have been reported in numerous studies as risk factors for PTSD (264–267).

Kay and colleagues provided an elegant discussion of the role of personality styles and characteristics as they relate to the experience of symptoms and the recovery from MTBI (268). They proposed three personality factors that may influence the development and maintenance of symptoms following MTBI: (a) individual response style to trauma, (b) emotional significance of a particular event for each person, and (c) vulnerable personality styles.

First, individuals tend to respond to the acute symptoms in different ways. Some individuals tend to over-emphasize cognitive and physical symptoms, whereas others tend to de-emphasize them. A certain symptom may be extremely debilitating for one person, yet another person may see this same symptom as simply slightly annoying. These response differences are not just determined by the differences in internal responses due to personality variables, but also by the environmental demands that challenge the person's ability to cope with that symptom. A laborer might be far less bothered by minor memory problems than a business-person, and an office worker might be only minimally concerned about mild balance problems compared to a roofer.

Second, there are differences in the emotional significance of a particular event for each person. Notwithstanding the emotional experience of the trauma itself, "for some persons the actual injury, the feelings evoked, and the response—or lack thereof—from others can trigger old, unresolved emotional issues. Often this takes the form of being vulnerable and unprotected, of not being responded to when hurt or sick, or of not being able to gain retribution when one has been wronged. Persons who grew up with significant holes in their emotional nurturing appear more at risk for responding in catastrophic ways to the emotional meaning of the injury" (p. 379–380) (268).

Third, based on their own clinical experience, Kay et al. proposed five different personality traits that they considered to be vulnerable to poor outcome following MTBI. These include: (a) overachievement, (b) dependency, (c) insecurity, (d) grandiosity, and (e) borderline personality characteristics (not disorder). Kay and colleagues explained the role of these traits as follows:

The *overachiever*, who is often obsessive-compulsive and derives his or her sense of self from driven accomplishment, is at risk for a catastrophic reaction when subtle cognitive slippage takes the edge off his or her performance. The *dependent person* is susceptible to being paralyzed by his or her symptoms. The experience of decreased efficacy dips him or her below the critical threshold of ability to cope independently and results in a behavioral freezing up that can become self-perpetuating. The *insecure person*, while sharing some of the same dynamics of the dependent person, also has the tendency to focus in on and therefore magnify his or her symptoms, thus adding another dimension to perpetuating dysfunction. *Grandiose persons* get into trouble by being so unable to acknowledge their decrease in ability that they deny it to themselves and others and continue to blunder into situations that evoke failure. The crash of self-esteem, when it comes, is usually catastrophic. The person with *borderline personality characteristics* (not disorder), an individual who is often high-achieving but unable to relate to others, is a prime candidate for significant personality disorganization at all levels after MTBI (Ref. 268, p. 379).

These vulnerable personality traits have received support in the literature by some researchers and clinicians who have provided case studies to highlight the importance of these premorbid personality traits (8). Ruff and colleagues present case discussions of four patients who sustained a MTBI, who they characterized as (a) grandiosity and narcissistic features, (b) borderline traits with recurrent depression, (c) over-achiever with perfectionist tendencies, and (d) unmet dependency needs. In line with Kay et al., Ruff and colleagues concluded that "For the individuals we presented, the resistance to recovery appears to have had its basis in unmet needs and trauma from early childhood. As adults these individuals developed psychological defenses which enabled them to have some of their previously frustrated needs met, which preserved them a sense of self-esteem. However, their prior needs and insecurities were reactivated by the MTBI" (p. 562).

Hibbard and colleagues (269) examined the frequency of personality disorders before and after sustaining a traumatic brain injury. Participants were 100 patients seen at least one year following a TBI ranging from mild to severe. Using a modified SCID-II interview to reflect pre-injury characteristics, 24% of the sample was diagnosed with pre-injury personality disorders. The most

common disorders were antisocial (15%) and obsessive-compulsive (6%) with incidence rates higher than community base rates reported in the literature. Higher rates of post-TBI personality disorders were found, with 66% of the sample meeting criteria for at least one personality disorder. The most common post-TBI disorders were borderline (26%), avoidant (26%), paranoid (17%), and obsessive-compulsive (24%). However, individuals with pre-TBI personality disorders were found to be at a greater risk of acquiring additional psychopathology post-TBI.

Evered and colleagues (48) examined the incidence and potential influences of emotional and personality problems in 129 patients with a history of MTBI and a presumed post-concussive disorder. The majority of patients (63.5%) met criteria for either Axis I and/or Axis II disorders, which is a rate of psychopathology that is higher than in the general public. The most common Axis II (i.e., personality) disorders were compulsive, histrionic, narcissistic, and dependent. This study clearly indicates that psychological problems, relating to personality and/or acute psychopathology, are prominent in patients with the presumed post-concussive disorder.

Greiffenstein and Baker (270) studied a unique sample of 23 patients involved in MTBI litigation (or disability evaluations) who had completed the MMPI prior to their injuries. They found that the majority of pre-injury MMPI profiles were abnormal in this group, with particular elevations on scales relating to physical symptoms, somatization, depression, and problems with thinking (i.e., Hs, D, Hy, and Sc scales; 83% to 87% of the sample had elevated scores on these scales). All 23 individuals had at least one elevated scale pre-injury, and 21 had two or more elevated scales pre-injury. Unexpectedly, when compared to their post-injury MMPI-2 profiles, their mean scores on the clinical scales pre-injury were actually *higher* than their mean scores post-injury. The highest mean scores post-injury were again the Hs, D, Hy, and Sc clinical scales (i.e., 74% to 100% of the sample with elevated scores on these scales). These findings suggest a very high prevalence of pre-injury psychopathology in this sample. However, the authors caution that there may have been a potential selection bias in this study towards sampling of patients (a) who were already abnormal, and (b) being worked up for past psychogenic contributions to medical complaints.

Although poorly understood, there is little doubt that personality characteristics influence the development and maintenance of the post-concussive disorder. These characteristics represent a large psychological component to the disorder. Other social-psychological factors, such as the nocebo effect, expectations, misattribution, the "good-old-days" bias, and diagnosis threat will be described in the next section.

### Social-Psychological Factors

Without question, social-psychological factors can have an enormous impact on the development and maintenance of the post-concussive disorder. There have been a small number of fascinating studies in this area illustrating the importance of these factors.

*Expectations and the Nocebo Effect.* Approximately 15 years ago, Mittenberg and colleagues discussed “expectations” as a partial explanation to account for elevated symptom reporting in patients who sustained MTBIs (74). Symptom reporting was examined in 223 community volunteers and 100 patients referred for neuropsychological assessment following a brain injury. The injured patients were asked to report the presence or absence of current symptoms and symptoms pre-injury. Community volunteers reported current symptoms and the symptoms they would *expect* to experience after sustaining a brain injury. Two important results emerged: (a) the number of symptoms reported by patients post-injury was the same as the number of symptoms healthy controls would *expect* to experience after a brain injury, and (b) patients with brain injuries consistently *underestimated* the normal prevalence of PCS-like symptoms in their retrospective accounts (i.e., their pre-injury symptoms) compared with the base rate of PCS symptoms reported by normal controls (i.e., their current symptoms). To explain these findings, Mittenberg and colleagues proposed that for some people the presence of PCS symptoms following MTBI may be due to “the anticipation, widely held by individuals who have had no opportunity to observe or experience post-concussive symptoms, that PCS will occur following mild head injury” (p. 202). Following an injury, a patient may “reattribute benign emotional, physiological, and memory symptoms to their head injury” (p. 203) and disregard or inaccurately recall their pre-injury symptom experience. For example, an individual may attribute a headache post-accident to the injury rather than due to a stressful day at work (271). This explanation has been termed *expectation as etiology*. Other researchers have reported similar, although not identical, results (271, 272).

People might “expect” to experience certain symptoms and problems, and this expectation might partially underlie symptom reporting following an MTBI. However, Gunstad and Suhr (271) emphasized the importance of appreciating a more generalized expectation of negative outcome regardless of the event (e.g., accident, injury, illness, or disease), consistent with the “nocebo effect.” The nocebo effect was introduced more than 40 years ago (273, 274) and research and discussion in this area has been ongoing (e.g., 275–281). The nocebo effect is the causation of sickness by the expectations of sickness and by associated emotional states. That is, the

sickness is, essentially, caused by expectation of sickness (282).

The nocebo effect in general, and expectations regarding symptoms and problems associated with MTBI in particular, likely represent significant psychological factors in the perception and reporting of symptoms in some patients. People’s retrospective perception of their past functioning also can influence their perception of their current functioning. For example, a person might falsely perceive a bigger difference than is actually the case between their past and present functioning due to overestimating past abilities or under-estimating past problems. This has been termed the “good-old-days bias.”

*“Good-Old-Days” Bias.* Researchers have reported that patients with back injuries, general trauma victims, as well as patients with head injury, overestimate the actual degree of change that has taken place post-injury by retrospectively recalling fewer pre-injury symptoms than the base rate of symptoms in controls (74, 271, 283–285). The *good-old-days* bias is a general response bias to view oneself as healthier in the past regardless of the presence or absence of brain injury and/or the experience of another negative event (e.g., an illness). The good-old-days bias seems to occur following a negative event (271, 284). As noted by Gunstad and Suhr (271), the “experience of any negative event, be it accident or illness, head injury or non-head-injury, may be required for one to focus on the past as ‘better’ than one’s current state, for one to think about the ‘good old days’ prior to the negative event” (p. 330).

The tendency of people to recall past symptoms and functioning more favorably than is actually the case is further complicated by involvement in personal injury litigation. Researchers have reported that plaintiffs tend to exhibit a *response bias* in symptom recall compared to non-litigants. That is, personal injury claimants free from head trauma tend to report a lower pre-accident prevalence of cognitive, mental, and emotional symptoms in their daily lives compared to non-litigants (e.g., 286, 287). Specifically, in a preliminary study, Lees-Haley and colleagues reported that personal injury claimants reported “better” past levels of functioning in life in general, self-esteem, concentration, and memory than general medical patients who were asked to provide retrospective ratings. The personal injury litigants also reported less depression, anxiety, irritability, and fatigue (287). These findings were replicated in a large-scale, multi-site study (286). In addition, personal injury litigants rated their premorbid work or school status, marriage, and relationships with their children as better than controls. This response bias, combined with an expectation of certain symptoms following MTBI, can have a potent impact on symptom reporting.

*Stereotype Threat and Diagnosis Threat.* Psychological factors also are relevant to understanding neuropsychological

test performance in people who are symptomatic long after an MTBI. For many years, researchers have been interested in the concept of *stereotype threat* to help explain performance differences between certain groups (e.g., 288–295). Research in this area is growing quickly (e.g., 296–301). The term *stereotype threat* was introduced by Steele (294) who defined this phenomenon as the “social-psychological threat that arises when one is in a situation or doing something for which a negative stereotype about one’s group applies. This predicament threatens one with being negatively stereotyped, with being judged or treated stereotypically, or with the prospect of conforming to the stereotype” (294, p. 614).

Stereotype threat, as a theory and psychological factor, suggests that an individual’s performance on a particular task can be negatively affected by the threat of an inferior and/or negative stereotype, such as men are superior to women in mathematics (288, 302). The adverse affect on performance is believed to be related to anxiety and/or a reduction of effort caused by the person’s negative expectations (294, 303). Research has supported the influence of stereotype threat as a partial explanation for why (a) women perform more poorly than men on mathematics tests (293, 295, 298), (b) African Americans perform more poorly on selected items from the Graduate Record Examination than Caucasians (288), and (c) Caucasians perform more poorly than Asians on mathematics tests (289). Similarly, stereotype threat is also thought to partially explain (d) the presence of memory and cognitive decline in aging (291, 296, 297), and (e) differences in intellectual performance in students stereotyped as intellectually inferior versus superior (300).

Suhr and Gunstad (302, 304) have conducted two innovative studies relating to stereotype threat with university students who suffered past MTBIs. Suhr and Gunstad (304) hypothesized that in people with MTBI, “calling attention to a personal history of head injury and its potential effects on cognition might lead to worse cognitive performance than that seen in individuals with similar head injury history, but who do not have attention called to either the head injury history or the possible consequences of head injury” (p. 450). This hypothesis was called *diagnosis threat*. Suhr and Gunstad (304) examined the effect of diagnosis threat on cognitive performance in 36 undergraduate students with a self-reported history of MTBI. Participants were assigned either to a diagnosis threat condition or a neutral condition. All participants completed a brief neuropsychological test battery. Prior to participation, subjects in the diagnosis threat condition were provided with information highlighting their “diagnosis” of head injury and the expected cognitive deficits associated with head injury.

Participants in the diagnosis threat condition performed worse on measures of intellectual ability, immediate memory, and delayed memory, but not on measures

of attention and psychomotor speed. Participants in the diagnosis threat condition rated themselves as putting forth less effort during testing, rated the tasks as more difficult, and felt they performed less well than participants in the neutral condition. In a follow-up replication study examining 53 undergraduate students with a history of self-reported MTBI, Suhr and Gunstad (302) reported that participants in the diagnosis threat condition performed worse on measures of memory, attention/working memory, and psychomotor speed. Contrary to the stereotype threat hypothesis however, differences in cognitive functioning between groups was not related to effort or anxiety.

The magnitude of the effect of diagnosis threat on neuropsychological test performance is not trivial. In fact, it’s alarming. The results from the Suhr and Gunstad (302, 304) studies are presented with the results from several meta-analytic studies in Figure 23-1. Quite remarkably, the psychological effect of “diagnosis threat” has a large, adverse effect on neuropsychological test performance. Notice that the adverse effect of an MTBI on neuropsychological test performance, when measured beyond the acute recovery period, is very small and virtually undetectable in group studies. In contrast, the adverse effect of diagnosis threat, in university students, is comparable to the adverse effects of depression and litigation on neuropsychological test performance.

### **Litigation Stress, Exaggeration, and Malingering**

Weissman (305) described aspects of litigation stress in the quote below. What is apparent from this quote is Weissman’s belief that litigation produces negative effects on the plaintiff’s mental state through multiple pathways, including greater susceptibility to stressors, attitude changes, motivational changes, and biases in self-reported problems.

Involvement in litigation renders plaintiffs susceptible to stressors and to influences that may lead to increased impairment, biased reportage, and retarded recovery. Underlying personality patterns play a critical role in defining and shaping reactions to trauma, to the stress of litigation, and to treatment interventions. Protracted litigation creates conditions that promote mnemonic and attitudinal distortions, as well as conscious and unconscious motivations for secondary gain. (Ref. 305, p. 67).

Plaintiffs with acquired brain injuries or psychological problems find themselves in a very different health care environment compared to injured or emotionally distressed people not in litigation. For example, individuals other than the injured person have a vested interest in the assessment and rehabilitation of the plaintiff. As well, others have a vested interest in doubting the veracity of

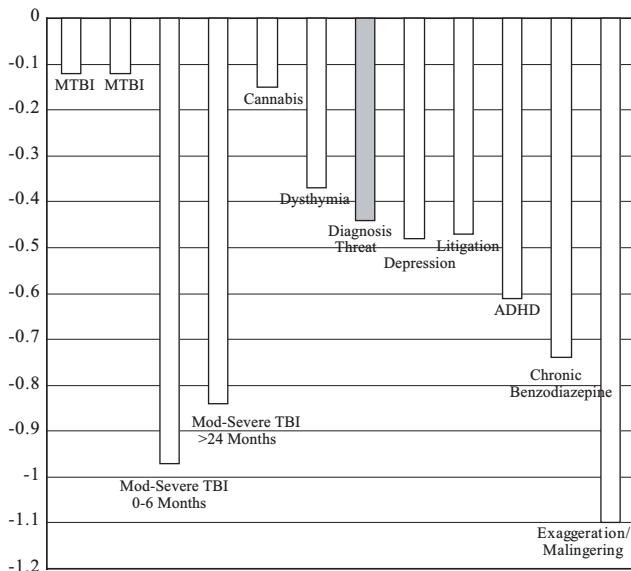


FIGURE 23-1

#### Effect sizes on overall neuropsychological functioning

*Note:* Effect sizes typically are expressed in pooled, weighted standard deviation units. However, across studies, there are some minor variations in the methods of calculation. By convention, effect sizes of .2 are considered small, .5 medium, and .8 large. This is from a statistical, not necessarily clinical, perspective. For this figure, the overall effect on cognitive or neuropsychological functioning is reported. The effect sizes are displayed in a negative direction to visually illustrate the “negative” or “adverse” effect on cognitive functioning. Effect sizes less than .3 should be considered very small and difficult to detect in individual patients because the patient and control groups largely overlap. First MTBI, moderate-severe TBI 0–6 months, >24 months, all in Schretlen & Shapiro (5), 39 studies,  $N = 1,716$  TBI,  $N = 1,164$  controls; second MTBI (338), 11 studies,  $N = 314$  MTBI,  $N = 308$  controls; Cannabis (339), long-term regular use, 11 studies,  $N = 623$  users,  $N = 409$  non or minimal users; Dysthymia, Depression, & Bipolar Disorder (340), 3 comparisons for dysthymia, 97 comparisons for depression, and 15 comparisons for bipolar disorder; Diagnosis Threat (302, 304), 2 studies, 23 comparisons; Litigation/financial incentives (55), 17 studies,  $N = 2,353$  total; ADHD (341), based on Full Scale IQ, 123 studies; Chronic benzodiazepine use (342), 13 studies,  $N = 384$ , 61 comparisons; Exaggeration/malingering (316), 32 studies published between 1985 and 1998, 41 independent comparisons

the patient’s health problems. The effect of these vested interests can be seen in the skepticism frequently attached to diagnoses of post-concussive disorder, post-traumatic stress disorder, or major depression; outside the context of litigation, these diagnoses are accepted with less skepticism.

One result of these vested interests and skepticism is that plaintiffs with alleged post-concussive disorder or psychological problems will be subjected to more intensive, frequent, and possibly hostile assessment of their

health problems. Thus, an individual seeking relief for symptoms while in litigation will experience a very different health care environment than will the person seeking such relief outside the context of litigation. In fact, there might even be pressures to avoid effective treatments and remain off work in order to illustrate the damages resulting from the cause of action. Undoubtedly, protracted litigation can be very stressful, and a plaintiff who was once significantly injured but who has largely recovered might feel *entitled* to the compensation anticipated by his lawyer, thus feeling *justified* in his decision to grossly exaggerate his current disability.

Exaggeration and/or malingering is believed to be a serious problem in disability evaluations and personal injury litigation relating to MTBI and the post-concussive disorder (306, 307). Hundreds of studies and reviews relating to the detection of exaggerated symptoms, poor effort during neuropsychological testing, and malingering have been published in the past 15 years. It is virtually impossible for clinicians to keep up with the research in this area. Fortunately, there are many good reviews of this literature (e.g., 308–318). Specific guidelines and recommendations for identifying malingering in a neuropsychological evaluation have been available for several years (319), and have recently been published for pain-related disability evaluations (320).

Malingering is the intentional production of false or greatly exaggerated symptoms for the purpose of attaining some identifiable external reward (41). It is important, however, to differentiate malingering from symptom exaggeration (which as discussed below, may have many possible explanations), the latter being embellishment of a symptom or sign that has a true physiological or psychological basis. In the presence of litigation, an individual may exaggerate symptoms. The person might exaggerate memory problems, concentration difficulty, depression, anxiety, pain, dizziness, sleep disturbance, or personality change. During neuropsychological testing, a person who is malingering (or for that matter exaggerating) is more likely to deliberately under-perform by consciously making errors, by not putting forth full effort, and/or by amplifying/fabricating complaints.

Resnick (321) described three types of malingering, labeled “pure malingering,” “partial malingering,” and “false imputation.” Pure malingering is characterized by a complete fabrication of symptoms. Partial malingering is defined by exaggerating actual symptoms or by reporting past symptoms as if they are continuing. False imputation refers to the deliberate misattribution of actual symptoms to the compensable event. Appreciating these types is important because mental health and legal professionals might have a simplistic view of malingering (i.e., only “pure malingering” is considered malingering).

Many lawyers and health care professionals adopt a rather extreme position regarding malingering. They



assume that malingering represents total fabrication (fraud). An example would be the person who pretends to not be able to walk who is videotaped walking. Less blatant malingering is conceptualized differently, such as “exaggeration.” Exaggeration is seen as common in personal injury litigation, and part of the function of the adversarial system is to illustrate to the trier of fact that exaggeration is present. Some professionals are tempted to believe that if a person has a well-documented psychiatric condition or visible brain damage on MRI that the person could not be malingering. However, it would be naïve to assume that a person with a psychiatric problem or the lingering effects of a traumatic brain injury could not malingering. That would be tantamount to concluding that people with these conditions are not capable of engaging in goal-directed behavior (e.g., exaggeration of symptoms to influence their litigation).

To conclude that a person might be malingering, the clinician must make an inference regarding a person’s underlying motivation or reasons for providing poor effort during neuropsychological testing, exaggerating symptoms or problems, and/or fabricating symptoms and problems. As seen in Figure 23-2, there are many possible underlying motivations for exaggeration (singly or in combination). The “cry for help” euphemism implies that the person has serious psychological or psychiatric problems and is desperately seeking recognition of, and attention for, these problems. There is a long history of conceptualizing exaggeration as a cry for help in psychology and neuropsychology, whereas in psychiatry and general medicine clinicians are inclined to attribute exaggeration to “psychological factors,” “psychiatric problems,” or “non-organic factors.” Second, in personal injury litigation, a person often feels angry about being injured and by perceived mistreatment from an insurance company. Some people feel justified in aggressively pursuing their litigation and feel entitled to generous compensation. Through a series of independent evaluations they might feel the need to exaggerate their symptoms or problems in order to be taken seriously, or to communicate how bad off they were in the past. There might be a number of secondary benefits relating to exaggerating one’s problems, such as attention from family and friends, or avoidance of unpleasant activities. Third, some people with depression have an extremely negative view of themselves, the world, and their future. This negativistic thinking can manifest in exaggeration of symptoms and problems. Some people have a personality style that is prone to dramatizing and exaggerating their problems. Fourth, a person might deliberately exaggerate because he has a deep-seated psychological need to be perceived as sick and disabled. The motivation is not the litigation, per se, but to be seen and treated as a sick and disabled person. Under these circumstances, the person would be diagnosed with a factitious disorder. Finally, a person

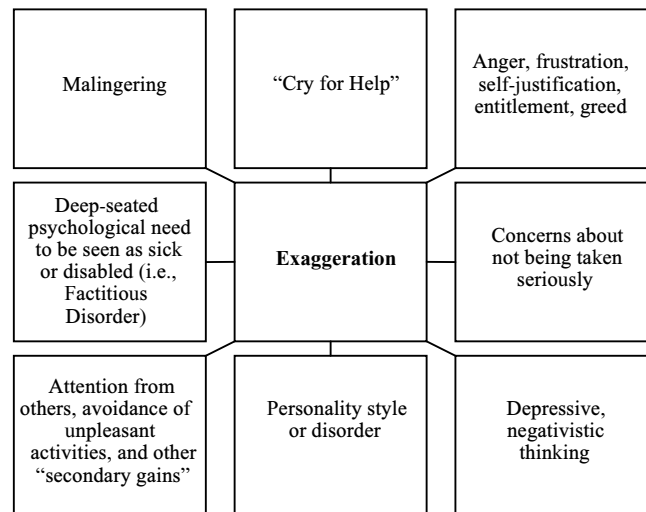


FIGURE 23-2

Possible reasons or motives for exaggeration

might deliberately exaggerate and/or under-perform during testing because he is trying to influence the outcome of his evaluations in order to influence the outcome of his litigation. This latter behavior is what we consider malingering.

In our experience, exaggeration is very common in people believed to have a persistent post-concussive disorder who are being evaluated in relation to a Worker’s Compensation claim, disability evaluation, or personal injury litigation. Malingering is much less common than exaggeration, and it would be a mistake to assume, without careful deliberation, that the exaggeration reflects malingering.

## CONCLUSIONS

There is no universally agreed upon etiology, pathophysiology, definition, or diagnostic criteria for the post-concussive disorder. Even the name of the syndrome/disorder varies in the literature (e.g., post-concussion syndrome, post-concussion disorder, and post-concussional disorder, to name a few). The disorder is assumed to be a direct and/or indirect consequence of an injury to the head or brain. However, a mild injury to the head or brain is not necessary (and often not sufficient) to produce the constellation of symptoms and problems that comprise this disorder. The symptoms and problems typically conceptualized as comprising the post-concussive disorder are non-specific; they can follow a mild injury to the brain or they can arise from other conditions, singly or in combination, such as chronic headaches, chronic bodily pain, depression, or post-traumatic stress disorder. These symptoms are also common in healthy, community-dwelling adults.

Following a mild traumatic brain injury, there is no doubt that most people experience a constellation of symptoms such as headaches, dizziness, fatigue, balance problems, sleep disturbance, difficulty thinking (e.g., concentration or memory), and/or emotional changes (e.g., irritability). These symptoms largely reflect the neurophysiology of concussion, which has been conceptualized as a multilayered neurometabolic cascade. The pathophysiology of this injury is largely reversible. However, under some circumstances people can have (a) macroscopic lesions, and/or (b) fairly widespread cellular damage or dysfunction (see the chapter by Iverson and colleagues in this book for a review).

Of course, not everyone experiences all symptoms, or symptoms to the same degree, but a core set of symptoms is commonly experienced. As a rule, these symptoms are at their worst in the first few days post-injury and they tend to get progressively better thereafter. This is illustrated in Figure 23-3. The data presented in Figure 23-3 represent a typical and common finding in the sport concussion literature and in clinical practice with concussed athletes. Athletes tend to report very high levels of symptoms and problems in the first few days post-injury, with relatively rapid resolution and recovery. Professional athletes seem to recover the fastest (322–325), followed by university athletes (30), and high school athletes (31, 326). This pattern reflects the reversible nature of the pathophysiology of mild concussions.

Trauma patients typically take longer to return to their baseline functioning. This is not surprising given that athletes tend to be young, healthy, highly motivated people with incentives to recover quickly and fully, and disincentives for having lingering problems. This creates a

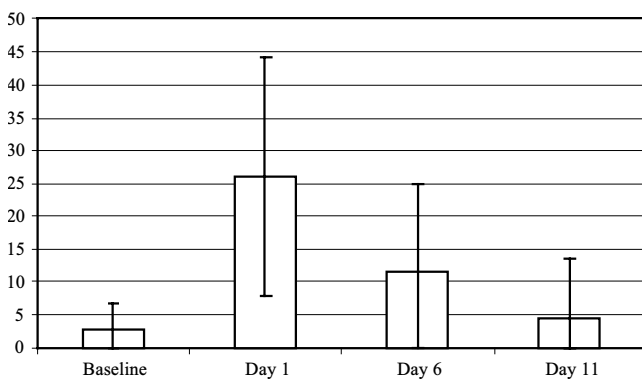


FIGURE 23-3

Total post-concussion symptom scores in concussed high school football players

Note: Total Post-Concussion Scale scores (mean and error lines equal one standard deviation) for 47 concussed high school football players tested preseason, within 4 days of injury ( $M = 1.7$ ,  $SD = .9$ ), within 8 days of injury ( $M = 5.5$ ,  $SD = 1.4$ ), and within 21 days of injury ( $M = 11.4$ ,  $SD = 3.6$ )

very different psychological perspective on the injury. In contrast, trauma patients often are older, less healthy, and they get injured under unexpected circumstances such as motor vehicle accidents, assaults, or work-place accidents. MTBIs sustained under these circumstances can be psychologically traumatic, and they can also occur in tandem with other physical injuries. A trauma patient might have significant personality characteristics, life stressors or circumstances, and/or pre-existing mental health or medical problems that complicate the expected recovery from an MTBI. A person with poor coping skills and vulnerable personality characteristics who has co-occurring depression, chronic pain, PTSD, or a combination of problems is virtually guaranteed to endorse many “post-concussion-like” symptoms even if he or she has fully recovered from the injury. It is very easy to misdiagnose a person with a co-morbid condition as having a persistent post-concussive disorder (which carries the assumption of brain damage or dysfunction as the etiology of the symptoms).

Without a doubt, an MTBI is *not necessary* for producing the constellation of symptoms and problems that comprise the persistent post-concussive disorder. The disorder is not specific to an injury to the head, brain, or both. Therefore, this disorder should be considered a diagnosis of exclusion. The clinician should carefully study the history and progression of the symptoms and problems, and systematically attempt to rule out the most obvious differential diagnoses or competing explanations for the symptoms (see Table 23-5 and Figure 23-4). Once identified, the differential diagnosis should be treated.

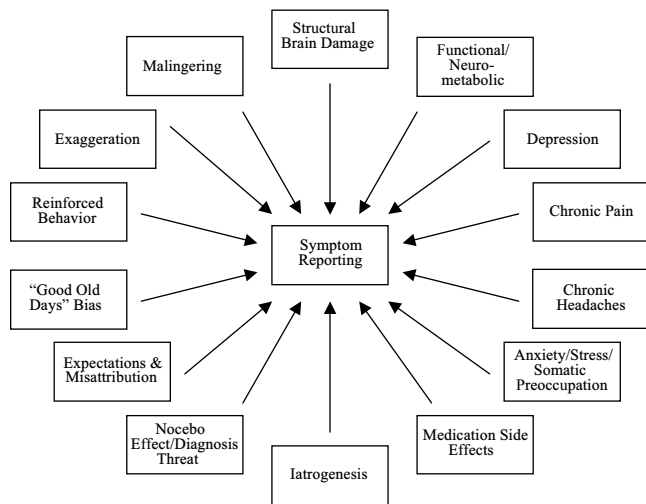
In our view, it is very unlikely that the post-concussive disorder simply reflects a neurological problem arising from a mild traumatic brain injury. The *initial* pathophysiology is, without question, neurological. From the beginning, however, there is great variability in how people respond psychologically to being injured and to experiencing symptoms and problems. Injured adults are psychologically-susceptible to the nocebo effect (expecting a negative outcome following a negative event) and misattribution of symptoms, and health care providers can inadvertently reinforce these factors. Some people are very psychologically vulnerable to developing chronic problems following an injury to their head, brain, body, or “psyche,” and the post-concussive disorder can be caused and maintained by factors that are entirely unrelated to permanent brain damage or dysfunction. In fact, in our view, the majority of people who appear to have the disorder (resulting from putative brain damage or dysfunction) actually have something else, such as depression or a combination of factors illustrated in Figure 23-4 (of course, a combination of factors might be the etiology for a post-concussive disorder).

People who sustain MTBIs characterized by structural damage on day-of-injury CT are, obviously, at

**TABLE 23-5**  
*Normal and Unusual Outcomes from MTBI*

2 WEEKS	2 WEEKS–3 MONTHS	3–6 MONTHS	6–12 MONTHS	1–3 YEARS
1. Recovery				
2. Symptoms/problems	Recovery			
3. Symptoms/problems	Partial recovery	Recovery		
4. Symptoms/problems	Partial recovery	Partial recovery	Recovery	
5. Symptoms/problems	Symptoms/problems	Partial recovery	Partial recovery	Recovery
6. Symptoms/problems	Symptoms/problems	Partial recovery	Partial recovery	Partial recovery
7. Symptoms/problems	Partial recovery	Worsening	Partial recovery	Recovery
8. Recovery	Worsening	Symptoms/problems	Partial recovery	Recovery
9. Symptoms/problems	Recovery	Worsening	Symptoms/problems	Symptoms/problems
10. Symptoms/problems	Symptoms/problems	Recovery	Worsening	Symptoms/problems
11. Symptoms/problems	Symptoms/problems	Recovery	Recovery	Symptoms/problems

Adapted with modifications from Iverson (4). The first four patterns represent the natural history of recovery from MTBI, in decreasing order of frequency. “Recovery” means few or no symptoms that are due to the biological effects of the original injury. The vast majority of concussed athletes and healthy adults with minor concussions in everyday life are represented by #1 (with very small numbers falling in patterns 2–11). The vast majority of trauma patients with *uncomplicated* MTBIs and no significant premorbid problems or comorbidities are represented by #1–3, with small numbers represented by pattern #4. The persistent post-concussive disorder is best illustrated by numbers 4–7 (psychological factors play a large role in maintaining symptom reporting). Numbers 8–11 represent patterns that frequently occur when a person is misdiagnosed with a persistent post-concussive disorder



**FIGURE 23-4**

Possible factors influencing symptom reporting acutely, post-acutely, and long after a mild traumatic brain injury

increased risk for permanent brain damage (i.e., those with “complicated” MTBIs). However, most of these patients do not develop a persistent post-concussive disorder. When they do, it is likely that several factors depicted in Figure 23-4 are operative (including permanent brain damage). The antiquated notion of a binary distinction between “organic and psychological” contributes to the long-standing disagreements and polarized perspectives relating to the post-concussive disorder. As is increasingly being demonstrated in diverse fields of

research, the “psychological” is often a link between biology and behavior. Do some people who appear to have the persistent post-concussive disorder have identifiable abnormalities on structural or functional neuroimaging? Of course they do. Does that mean that the abnormalities are the *predominant* underlying cause of the disorder? Of course not (but they might be major or minor contributors to the symptom presentation). Adopting a biopsychosocial perspective is the only reasonable way to have a comprehensive, unbiased understanding of this disorder.

In clinical and forensic practice, diagnosing someone with a persistent post-concussive disorder implies directly or indirectly that the person has “brain damage.” This is a relief to a small number of patients seeking an explanation for their perceived problems. For many patients, however, it can have serious iatrogenic implications. The diagnosis can cause them to worry, dwell, and become focused on the belief that their brain is damaged. The diagnosis can be counter-therapeutic, reinforcing the misattribution of all symptoms to brain damage and leading to a sense of hopelessness regarding treatment and future improvement. According to the ICD-10 diagnostic criteria for the syndrome, one of the cardinal features is a preoccupation with symptoms and fear of brain damage with hypochondriacal concern and adoption of a sick role.

In our experience, the post-concussive disorder is over-diagnosed and frequently misdiagnosed. By over-diagnosed, we mean that there is often an assumption that a symptomatic person with a remote MTBI is suffering from brain damage that largely underlies the perceived

and reported symptoms. This assumption of brain damage carries a very negative prognosis and tends to inhibit attempts at treatment. Although it might be true in some patients, for most people the original injury to the brain has *mostly* resolved and the disorder represents, in large part, an entrenched psychological disorder. By misdiagnosed, we mean that the person is actually suffering from something else, such as chronic pain, depression, or PTSD, which is misdiagnosed or co-diagnosed.

Of course, it is also possible that the diagnosis of post-concussive disorder can be missed. We have seen cases in the first three months post-injury where the treating clinician has diagnosed depression or PTSD when it seemed more likely that the patient was suffering from symptoms and problems arising predominately from the biological and psychological consequences of his or her MTBI.

So, what is the post-concussive disorder? The literature to date does not allow us to determine whether it is a single disorder, a spectrum disorder, or a group of disorders. The literature does not allow us to determine the degree to which abnormal brain physiology underlies some or all of the symptoms and problems associated with the disorder. There is no way to reliably differentiate the post-concussive disorder from depression, and it is possible that the disorder is a depression-spectrum disorder. In its “true” form, the post-concussive disorder arises as a direct *and* indirect consequence of mild injury to the brain (assuming it is not frankly misdiagnosed sometime long after an MTBI). When it manifests early and is maintained chronically the condition is almost always biopsychosocial. The “biological,” the “psychological,” and the “social” are all potentially treatable<sup>7</sup>. In our view, it is a mistake to conceptualize patients with the post-concussive disorder as if they are simply less “serious” versions of patients with severe traumatic brain injuries. These are distinct patient populations with distinct treatment and rehabilitation needs.

Ideally, clinicians and researchers should try to prevent the development of, or treat, the post-concussive disorder. There is evidence that early intervention, as simple as education and reassurance, is helpful for reducing the number and severity of symptoms experienced in the initial weeks and months post-injury (see the chapter by Iverson et al. for a review). This education, reassurance, and problem-solving should occur in the first two weeks post-injury.

When patients appear to have a *persistent* post-concussive disorder, differential treatment often flows from

<sup>7</sup> Unfortunately, when treatment is offered it typically does not involve a broad-spectrum biopsychosocial approach, with an emphasis on identifying and addressing the diverse factors that underlie the ongoing symptoms and problems. Without this approach, the treatment is likely to be unsuccessful. Ineffective treatment contributes to the belief that the post-concussive disorder is “permanent.”

differential diagnosis. Given the clear overlap between the symptoms of depression and post-concussive disorder, some researchers have recommended treatment with antidepressants (327–330) or cognitive behavior therapy (331, 332). Medications and psychotherapy would be an obvious choice, of course, if depression is simply mimicking the post-concussive disorder. Those recommending cognitive behavior therapy have set forth a treatment protocol that is based on those principles but is tailored toward the post-concussive disorder and belief systems relating to symptoms and brain damage.

We believe that the post-concussive disorder is *treatable* in the majority of patients. The first step is to identify whether a person really has it, or whether his or her symptoms and problems are more appropriately attributable to something else (thus, differential diagnosis leading to differential treatment). If the person is believed to be suffering from a post-concussive disorder, then general mental health and specific “symptomatic” treatment is indicated. Symptomatic treatment involves treating depression and anxiety, improving sleep, reducing stress, facilitating adaptive coping, helping the patient problem-solve life stressors, increasing exercise, and promoting a resumption to a more active and normal lifestyle.

Our research group (GLI) is in the process of piloting a new psychological treatment program for patients with persistent post-concussive disorder. This program arises from Contextual Behavior Therapy and Acceptance & Commitment Therapy (ACT; 333, 334). This approach has been successfully used with several clinical populations (e.g., depression, anxiety, stress, and substance abuse), as well as very difficult patients with chronic pain (335–337). Acceptance and Commitment Therapy is based on the idea that psychological suffering is usually caused by experiential avoidance, cognitive entanglement (i.e., “cognitive fusion”), and the resulting failure to take needed behavioral steps that are consistent with core values. This treatment approach takes the view that simply trying to change problematic thoughts and feelings as a means of coping might be relatively unhelpful. In contrast, powerful alternatives are available, including acceptance, mindfulness<sup>8</sup>, cognitive defusion (learning to see thoughts as thoughts), value clarification, and committed values-based action. The treatment program includes components of traditional cognitive-behavioral therapy, and it includes psychoeducation

<sup>8</sup> Mindfulness-based Cognitive Therapy, based largely on the work of Jon Kabat Zinn, includes simple breathing meditations and yoga stretches to help patients become more aware of the present moment, including getting in touch with moment-to-moment changes in the mind and the body. This therapy also includes basic education about depression, anxiety, and stress, and several exercises from cognitive therapy that show the links between thinking and feeling. The approach is closely linked to the Eastern insight meditation tradition that has been taught for two thousand years.

relating to the social-psychological factors that influence the perception and attribution of symptoms (e.g., nocebo effect, misattribution, and the “good-old-days” bias, as depicted in Figure 23-4).

To date, most attention in the literature has been devoted to describing characteristics or predictors of the post-concussive disorder, or debating its existence or etiology. It is our hope that researchers increasingly will turn their attention to treatment designed to reduce patient's suffering and improve their real-world functioning.

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**APPENDIX A**  
**British Columbia Post-Concussion Symptom Inventory (BC-PSI)**

**BC-PSI**

Name: \_\_\_\_\_

Date: \_\_\_\_\_

The following is a list of symptoms that you may have experienced. Please rate each symptom or problem in regards to how often it happens and how bad it is. Consider your experience with these symptoms or problems over the past two weeks, including today.

**HOW OFTEN**

**HOW BAD**

*(Frequency)*

- 0 = Not at all
- 1 = 1-2 times
- 2 = Several times
- 3 = Often
- 4 = Very often
- 5 = Constantly

*(Intensity)*

- 0 = Not at all
- 1 = Very mild problem
- 2 = Mild Problem
- 3 = Moderate problem
- 4 = Severe problem
- 5 = Very severe problem

**SYMPTOMS & LIFE PROBLEMS**

**HOW OFTEN**

**HOW BAD**

- |                              |       |       |
|------------------------------|-------|-------|
| 1. Headaches                 | _____ | _____ |
| 2. Dizziness/light-headed    | _____ | _____ |
| 3. Nausea/feeling sick       | _____ | _____ |
| 4. Fatigue                   | _____ | _____ |
| 5. Extra sensitive to noises | _____ | _____ |
| 6. Irritable                 | _____ | _____ |
| 7. Feeling Sad               | _____ | _____ |
| 8. Nervous or tense          | _____ | _____ |
| 9. Temper problems           | _____ | _____ |
| 10. Poor concentration       | _____ | _____ |
| 11. Memory problems          | _____ | _____ |
| 12. Difficulty reading       | _____ | _____ |
| 13. Poor sleep               | _____ | _____ |

14. Does alcohol affect you more than in the past?

- |            |   |          |   |           |
|------------|---|----------|---|-----------|
| 1          | 2 | 3        | 4 | 5         |
| Not at all |   | Somewhat |   | Very Much |

15. Do you find yourself worrying and dwelling on the symptoms above?

- |            |   |          |   |           |
|------------|---|----------|---|-----------|
| 1          | 2 | 3        | 4 | 5         |
| Not at all |   | Somewhat |   | Very Much |

16. Do you believe you have damage to your brain?

- |            |   |          |   |           |
|------------|---|----------|---|-----------|
| 1          | 2 | 3        | 4 | 5         |
| Not at all |   | Somewhat |   | Very Much |

**APPENDIX B**  
**Scoring Template for the BC-PSI**

**SYMPTOM CLASSIFICATION**

<b>SYMPTOM/PROBLEM</b>	<b>PRODUCT</b>	<b>ITEM SCORE</b>	<b>NONE</b>	<b>MILD</b>	<b>MODERATE</b>
Headaches					
Dizziness/light-headed					
Nausea/feeling sick					
Fatigue					
Extra sensitive to noises					
Irritable					
Sad					
Nervous or tense					
Temper problems					
Poor concentration					
Memory problems					
Difficulty reading					
Poor sleep					
Total Score	—		—	—	—

**Step 1:** Multiply the frequency rating by the severity rating and enter value in the “Product” column (e.g., 2 x 3 = 6).  
**Step 2:** Convert product score to “Item Score” based on the following: Product = 0–1, Item score = 0; Product = 2–3, Item Score = 1; Product = 4–6, Item Score = 2; Product = 8–12, Item Score = 3; Product = 15+, Item Score = 4. Enter the Item scores into the grid. **Step 3:** Sum the Item Scores for the Total Score. **Step 4:** Place an “X” in the appropriate classification range for each symptom based on the following “Item Score” criteria: 0 = None, 1–2 = Mild, and 3+ = Moderate or greater. Total Scores: 0 = “Low”, 1 – 9 = “Normal”, 10 – 14 = “Unusually High”, and 15+ = “Extremely High” relative to *healthy adults*.

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# 24

## Sport-Related Concussion

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**C**oncussion is a common injury in sport (1–11). Moreover, these injuries might be more prevalent than initially thought because some concussions may go unrecognized (12). Injuries without loss of consciousness (LOC) occur most frequently; in fact, approximately 90% of concussions in sport occur without LOC (13–15). Because most concussions lack the dramatic on-field nature of those with LOC, they are typically more difficult to detect and might be under-diagnosed by sports medicine practitioners (16). The importance of accurate diagnosis, management, and return-to-play decisions extends from the elite ranks of professional athletes to the child or adolescent athlete. This chapter, designed to be a comprehensive overview, is divided into the following eight sections: (a) definition of concussion, (b) pathophysiology, (c) injury severity markers (signs), (d) symptoms, (e) structural and functional neuroimaging, (f) neuropsychological outcome, (g) cumulative effects, (h) recovery time and return to play decision-making, and (i) conclusions.

### DEFINITION OF CONCUSSION

There has not been a universally-accepted definition of concussion. Traditionally, the most widely accepted definition has been that proposed by the Committee on

Head Injury Nomenclature of Neurological Surgeons in 1966 (17). That committee defined concussion as: “a clinical syndrome characterized by the immediate and transient post-traumatic impairment of neural function such as alteration of consciousness, disturbance of vision or equilibrium, etc., due to brain stem dysfunction.”

More recently, many clinicians and researchers currently use the definition of concussion described by the American Academy of Neurology (AAN): “Concussion is a trauma-induced alteration in mental status that may or may not include a loss of consciousness” (18, p. 582). This definition was prompted by the belief of the AAN definition authors that previous definitions may be too limiting because the injury is not restricted to the brain stem and may involve other brain structures (e.g., cortical areas). This definition also served to emphasize the fact that concussion may occur with or without a loss of consciousness.

In 2001, and most recently in 2004, an International Symposium on Concussion in Sport was held where concussion experts from around the world met to discuss specific issues related to the injury. One major outcome of these symposia was the adoption of a global definition of concussion that improved upon previous definitions. The current definition is as follows: “Sports concussion is defined as a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces”



(19, p. 196). In addition to this definition, the features listed below were outlined.

1. "Concussion may be caused either by a direct blow to the head, face, neck, or elsewhere on the body with an "impulsive" force transmitted to the head.
2. Concussion typically results in the rapid onset of short-lived impairment of neurological function that resolves spontaneously.
3. Concussion may result in neuropathological changes, but the acute clinical symptoms largely reflect a functional disturbance rather than structural injury.
4. Concussion results in a graded set of clinical syndromes that may or may not involve loss of consciousness. Resolution of the clinical and cognitive symptoms typically follows a sequential course.
5. Concussion is typically associated with grossly normal structural neuroimaging studies." (19, p. 196)

### PATHOPHYSIOLOGY

The pathoanatomy and pathophysiology of mild traumatic brain injury (MTBI) is reviewed, in detail, in the mild traumatic brain injury chapter in this book. In that chapter, it was described that brain injuries produced by acceleration/deceleration forces occur along a continuum of severity dependent upon the mechanical forces that caused them (20, 21). Concussion in athletes is typically produced by acceleration/deceleration forces (e.g., helmet to helmet contact in North American football or helmet to ice contact in ice hockey). Concussion can be considered an injury at the mild end of the MTBI continuum with LOC (when it occurs) and posttraumatic amnesia being considerably more brief in duration, and with low levels of axonal stretch. This limited axonal stretching can initiate a pathophysiologic process that leads to very limited cell death (largely dependent on the morphology of the cell) but in the vast majority of cells leads to a reversible series of metabolic events.

Giza and Hovda (22) describe the complex interwoven cellular and vascular changes that occur following concussion as a multilayered neurometabolic cascade. The primary mechanisms include ionic shifts, abnormal energy metabolism, diminished cerebral blood flow, and impaired neurotransmission. A brief summary of this process, derived from several sources (22, 23), is provided below.

Stretching of an axon results in an indiscriminate release of neurotransmitters and uncontrolled ionic fluxes. When ionic gradients are disrupted, cells respond by activating ion pumps in an attempt to restore the normal membrane potential. Pump activation increases glucose utilization. This contributes to dramatic increases in the local cerebral metabolic rate for glucose. This

hypermetabolism occurs in tandem with decreased cerebral blood flow, which contributes to the disparity between glucose supply and demand. There also appears to be impaired oxidative metabolism and diminished mitochondrial function, resulting in the over-utilization of anaerobic energy pathways and elevated lactate as a by-product. Moreover, intracellular magnesium levels appear to decrease significantly and remain depressed for several days following injury. This is important because magnesium is essential for the generation of adenosine-triphosphate (ATP – energy production). Magnesium is also essential for the initiation of protein synthesis and the maintenance of the cellular membrane potential. A sustained influx of  $Ca^{2+}$  can result in mitochondrial accumulations of this ion contributing to metabolic dysfunction and energy failure. High intracellular  $Ca^{2+}$  levels, combined with stretch injury, can initiate an irreversible process of destruction of microtubules within axons.

Fortunately, the brain undergoes a dynamic restorative process in the initial days to weeks following a concussion. From a commonsense perspective, the ionic shifts, abnormal energy metabolism, diminished cerebral blood flow, and impaired neurotransmission believed to be associated with concussions in sports reinforces the importance of immediate rest following injury. Although not established empirically, it seems reasonable to assume that vigorous exercise or hard physical contact might exacerbate the pathophysiology described above.

### INJURY SEVERITY MARKERS (SIGNS)

Appropriate acute care and management of the concussed athlete begins with a detailed and accurate assessment of the severity of the injury. As with any serious injury, the first priority is always to evaluate the athlete's level of consciousness and ABCs (airway, breathing, and circulation). The attending medical staff must always be prepared with an emergency action plan in the event that the evacuation of a critically head-or neck-injured athlete is necessary. This plan should be familiar to all staff, be well delineated, and frequently rehearsed.

#### Loss of Consciousness

Upon ruling out more severe injury via neurological and clinical examination, the acute evaluation continues with the assessment of concussion. First, the clinician should establish whether a loss of consciousness (LOC) has occurred. By definition, LOC represents a state of brief coma in which the eyes are typically closed and the athlete is unresponsive to external stimuli. LOC is relatively uncommon and reportedly occurs in less than 10% of concussive injuries in most (13–15), but not all (24) studies. Moreover, prolonged LOC (>1–2 minutes) in sport-related

concussion occurs much less frequently. Athletes with LOC are typically unresponsive for only a brief period of time, sometimes only one to two seconds. This may at times make LOC difficult to identify because the response of medical personnel to injured athletes is beyond this time window.

Although many of the concussion grading and management scales rely heavily upon the presence or absence and duration of loss of consciousness, research on the relation between LOC and outcome is mixed. Large scale studies with trauma patients have not revealed a relation between LOC and neuropsychological outcome (e.g., 25, 26). Some researchers examining athletes with concussions have reported an association between LOC and immediate or short-term outcome (e.g., 24, 27, 28), while others have not (e.g., 29, 30).

### Confusion

A more common form of mental status change following concussion involves confusion and amnesia. Confusion (i.e., disorientation), by definition, represents impaired awareness and orientation to surroundings, though memory systems are not necessarily directly affected. An athlete with post-injury confusion will typically appear stunned, dazed, or “glassy-eyed” on the sideline or playing field. Confusion is often manifested in athletes who do not remove themselves from play in the form of difficulty with appropriate play-calling, failure to correctly execute their positional assignment during play, or difficulty in communicating game information to teammates or coaches. Teammates are often the first to recognize that an athlete has been injured when the athlete shows these behaviors and has difficulty maintaining the flow of the game. On the sidelines, confused athletes may answer questions slowly or inappropriately, ask “what is going on” or “what happened,” and may repeat himself or herself during evaluation. Some may be temporarily disoriented to time or place, and even, very rarely, to people they know well (e.g., not knowing coaches or teammates). To properly assess the presence of confusion, medical personnel can ask the athlete simple orientation questions such as the date, and names of the stadium, city, and opposing team. Please see Table 24-1 for a list of orientation questions extracted from the University of Pittsburgh Medical Center’s Concussion Card.

### Amnesia

Amnesia is emerging as perhaps the most important sign to carefully assess following concussion (after more serious injuries have been ruled out). Amnesia due to concussion may present as retrograde amnesia (difficulty with memory of events prior to the injury) or post-traumatic/ anterograde amnesia (difficulty with memory for events

following the injury). Both forms of amnesia should be assessed thoroughly. Athletes who present with one or both types of amnesia may initially have difficulty recalling large spans of time before the injury, after the injury, or both. These larger periods of amnesia typically shrink as the injury becomes less acute. The presence and duration of amnesia, disorientation, or mental status disturbance has been associated with immediate outcome or slower recovery (24, 28, 29, 31, 32) in many, but not all studies (e.g., 30).

Post-traumatic amnesia and anterograde amnesia are synonymous terms that represent the duration of time between the head trauma (for example, an ice hockey player’s forehead striking the boards) and the point at which the athlete reports a return of normal continuous memory functioning (e.g., remembering the athletic trainer asking the athlete orientation questions in the locker room). One method for assessing post-traumatic confusion and amnesia is provided in Table 24-1 (UPMC Concussion Card Mental Status Testing).

At times, especially during a sideline assessment, confusion and post-traumatic amnesia may be difficult to disentangle. It is important to remember that confusion is not necessarily associated with a loss of memory, whereas

**TABLE 24-1**

*University of Pittsburgh Medical Centers’  
Sideline Concussion Card: Acute (sideline  
or on-field) Mental Status Testing*

**On-Field Cognitive Testing**

Orientation (ask the athlete the following questions)

- What stadium is this?
- What city is this?
- Who is the opposing team?
- What month is it?
- What day is it?

*Post-Traumatic Amnesia (ask the athlete to repeat the following words)*

- Girl, dog, green

*Retrograde Amnesia (ask the athlete the following questions)*

- What happened in the prior quarter or half?
- What do you remember just prior to the hit?
- What was the score of the game prior to the hit?
- Do you remember the hit?

*Concentration (ask the athlete to do the following)*

- Repeat the days of the week backward, starting with today
- Repeat these numbers backward (63) (419)

*Word list memory*

- Ask the athlete to repeat the three words from earlier (girl, dog, green)

amnesia is only present with a loss of memory. This memory loss may span only a few seconds or minutes. It sometimes can span several hours, but rarely exceeds a day. A practitioner may be unable to differentiate confusion and amnesia until the athlete's confusion has resolved. Only then can memories surrounding the injury actually be discussed. Once the athlete is more lucid, the practitioner may gain additional insight into any existing post-traumatic amnesia by asking the athlete to recall the events that occurred immediately following the trauma (e.g., rising from the ground, walking/skating to sideline, memory for any part of the game played or observed after the injury, memory for the score of the contest, memory of the ride home, and so on). Post-traumatic amnesia is inferred by failure to remember events following the injury.

Retrograde amnesia is defined as the inability to recall events before the head trauma. Commonly used questions to assess retrograde amnesia are presented in Table 24-1. Medical personnel may ask for the athlete's memory of the actual injury (e.g., seeing a linebacker charge toward him with his helmet down, then falling backward and striking the back of his head to the ground). Then, additional questions can probe events that are increasingly remote from the injury (e.g., the score at the beginning of the first quarter, coming onto the field for stretching exercises, and getting dressed in the locker room). The length of retrograde amnesia will typically "shrink" over time. As recovery occurs, the period of retrograde amnesia may shrink from several minutes to a few seconds (in rare cases an athlete will have retrograde amnesia for hours or days). The presence and duration of retrograde amnesia has been associated with worse initial presentation and with slower recovery (27–29, 31).

## SYMPTOMS

The initial signs and symptoms of concussion vary from athlete to athlete, depending on the biomechanical forces

involved, specifically-affected brain areas, athletes' prior history of injury, and other factors. A summary of common on-field signs and symptoms of concussion is presented in Table 24-2. It is important to note that an athlete may present with as few as one symptom of injury or potentially a constellation of symptoms.

Headaches and dizziness are the most commonly reported symptoms of injury (9, 13). Moreover, headaches lasting more than three hours post injury (27), those present at seven days post injury (32), or those that are migraine-like (33) have been associated with slow recovery. However, the absence of headache does not rule out a concussion, highlighting the importance of a thorough assessment of all symptoms. Assessment of post-concussion headache may be complicated by the presence of musculoskeletal headaches and other pre-existing headache syndromes (e.g., migraine disorder or frequent stress headaches).

Most frequently, a "concussion headache" is described as a sensation of pressure in the skull that may be localized to one region of the head or may be generalized in nature. In some athletes (particularly athletes with a history of migraine), the headache may take the form of a vascular headache, may be unilateral, and is often described as throbbing or pulsating. The headache may not develop immediately after injury and may develop in the minutes, or even hours, following injury. Therefore, it is important to question the potentially concussed athlete regarding the development of symptoms beyond the first few minutes after injury. Post-concussion headache is often worsened with physical exertion. Thus, if the athlete complains of worsening headache during exertional testing or return to play, post-concussion headache should be suspected and conservative management is indicated. While headache following a concussion usually does not constitute a medical emergency, a severe or progressively severe headache, particularly when accompanied by vomiting or rapidly declining mental status, may signal a life-threatening situation such as a subdural hematoma or

**TABLE 24-2**

*University of Pittsburgh Medical Center's Sideline Concussion Card: Signs and Symptoms of Concussion*

SIGNS OBSERVED BY STAFF	SYMPTOMS REPORTED BY ATHLETE
Loses consciousness	Feeling "foggy" or groggy
Forgets events prior to play (retrograde)	Change in sleep pattern (appears later)
Forgets events after hit (post-traumatic)	Feeling Fatigued
Appears to be dazed or stunned	Headache
Is confused about assignment	Nausea
Forgets plays	Balance problems or dizziness
Is unsure of game, score, or opponent	Double or fuzzy/blurry vision
Moves clumsily	Sensitivity to light or noise
Answers questions slowly	Feeling sluggish or slowed down
Shows behavior or personality change	Concentration or memory problems

intracranial bleed. This should prompt immediate transport to hospital and a CT scan of the brain.

In addition to headaches, many other symptoms may emerge as a result of concussive injury. For example, athletes will commonly experience blurred vision, changes in peripheral vision, or other visual disturbance. Moreover, an athlete may report increased fatigue, “feeling a step slow,” or feeling sluggish. Fatigue is especially prominent in concussed athletes in the days following injury and this symptom may be as prominent as headache. Also, athletes may report cognitive changes, including problems with attention, concentration, short-term memory, learning, and multitasking. These symptoms sometimes become more noticeable after the athlete has returned to school or work.

Another frequently reported symptom which has gained recent research attention is a reported sensation of feeling “foggy” following concussion (34). In this study, a sample of concussed high school students who endorsed feeling “foggy” on a symptom inventory were compared to concussed high school athletes who did not endorse a sense of “fogginess.” At one-week post injury, the foggy group demonstrated significantly slower reaction times, attenuated memory performance, and slower processing speed via computerized neurocognitive testing. In addition, the “foggy” athletes also endorsed a significantly higher number of other post-concussion symptoms when compared to the group who did not endorse fogginess.

Another commonly reported or observed symptom is that of emotional changes. Most often, athletes will report increased irritability, or having a “shorter fuse.” However, other emotional changes may occur such as sadness/ depression, nervousness/ anxiety, or even (much less commonly) silliness or euphoria. Affect may be described by the athlete or parent as flattened or labile. Emotional changes may be very brief (e.g., a linebacker bursts into tears for 30 seconds on the sideline) or may be prolonged in the case of a more significant injury (athlete reports persistent depression).

### STRUCTURAL AND FUNCTIONAL NEUROIMAGING

Given that concussion is largely a metabolic and not a structural injury, traditional neuroimaging techniques such as CT or MRI are almost always unremarkable following a single concussion. Despite this fact, these techniques are useful for ruling out more serious pathology (e.g., cerebral bleed or skull fracture) that occasionally occur in sports-related head injuries. Athletes most likely to show abnormalities on structural neuroimaging are boxers. This is not particularly surprising because historically damage could be seen with the naked eye at

autopsy (35). Studies on professional boxers, active and retired, have revealed the greatest number of CT abnormalities estimated to be between 25–50% (36–39). In these boxers, a cavum septum pellucidum was considered a CT sign of traumatic encephalopathy (40). CT abnormalities were correlated with the number of bouts fought (41) and were estimated to be less frequently observed in amateur boxers [between 0 and 20% had abnormalities (42–44)]. In addition to boxing, Sortland and Tysvaer (45) reported that approximately 33% of a sample of retired Norwegian international soccer players had widening of the lateral ventricles suggesting some form of generalized cerebral atrophy.

Magnetic resonance imaging (MRI) studies on boxers show a similar pattern of results as those using CT with the exception that MRI was able to detect subdural hematoma, white matter changes, and focal contusion not detected using CT (38, 46). MRI studies on young or amateur boxers consistently showed no change as a result of participation in their sport (42, 47, 48).

Recently, functional MRI (fMRI) and blood oxygen level dependent (BOLD) activity has been used to learn about the functional changes that can occur following concussion. One study compared symptomatic concussed athletes to a university student sample using a working memory task. Concussed athletes had areas of decreased activation compared to controls, such as the mid-dorsolateral prefrontal cortex. In addition, there was activation of regions beyond those of the control subjects in both temporal and parietal lobes (49). A prospective study on a small number of concussed athletes revealed differences from baseline brain activity using a number of cognitive tasks. Specifically, there was an increase in regions that were activated compared to baseline with greater signal intensity in these areas compared to baseline. Concussion induced differences in neural functioning were observed in the absence of behavioral deficits (50). These two small fMRI studies differed in methodology (between versus within subject designs) and in some of the results provided. There were two similarities: (a) Concussed athletes had a greater number of brain regions activated following concussion than did non-injured controls or the same athletes at baseline. This finding is consistent with recruitment of brain areas beyond those normally expected following concussion. (b) Both studies showed areas with greater levels of activation following concussion, however, Chen et al. reported a reduction in frontal lobe activity associated with working memory.

There are also few positron emission tomography (PET) and single photon emission computerized tomography (SPECT) studies on concussed athletes. The limited data on concussion in athletes suggests a pattern of frontal hypoactivation following injury. In amateur boxers, rCBF values were reported to be within the normal range while professional boxers had flow values that were

below normal (51), especially in frontocentral regions (52). Other studies have revealed hypoperfusion in boxers (53). In general, there are differences in subjects and methodologies across studies that likely contribute to some of the discrepant findings. Nonetheless, there is some consistency across studies on blood flow following concussion suggesting hypoperfusion in the frontal lobes.

The electroencephalogram (EEG) has also been used to study concussion in athletes. Standard clinical EEG assessments revealed abnormalities associated with several years of involvement in boxing and soccer (e.g., 54–56). More recently, preliminary evidence for amplitude reductions across all standard frequency bands, especially during standing postures, were reported in 12 recently concussed athletes who were asymptomatic at the time of assessment (57). Similar reductions in gamma band activity were observed during a movement paradigm requiring a 50% maximal voluntary contraction (58).

In addition to EEG, there are a growing number of cognitive event-related potential (ERP) studies on concussed athletes. Although preliminary, the results suggest that these techniques may be of considerable benefit for the assessment of a single concussive event. One of the ERPs used in these studies was the N2/P3 or P300 response, a series of averaged EEG responses time-locked to a stimulus, with positive or negative peaks associated with different cognitive processes. P3 peak amplitude is believed to index allocation of attention (59, 60), while latency is related to stimulus evaluation and categorization time (61), transfer of information to consciousness and memory systems (60), and stimulus saliency (62).

Studies that used an auditory P3 paradigm have yielded mixed results. In one of these studies, five boxers were examined before and after a fight. Although several of the peaks showed no change in latency or amplitude, decreased amplitude was observed for the N2b peak (which precedes the P3 response) following the fights (63). Another study on amateur boxers reported no differences for auditory P3 latency or amplitude (64). In contrast, visual N2/P3 studies have yielded more consistent findings (65). In concussed athletes that were symptomatic, significant reductions in visual P3 amplitude were reported compared to recently concussed but asymptomatic athletes and never concussed athletes (66, 67). In addition, longer visual P3 peak latencies were correlated with self-reported attention and memory deficits in athletes with three or more concussions (68).

ERPs that precede movement have also been used experimentally to assess concussion in athletes. One of these studies showed negative results (68). Others have reported preliminary evidence for amplitude reductions using small numbers of concussed athletes in using a postural paradigm (69) and a movement paradigm requiring a 50% maximal voluntary contraction (58). Therefore, the electrophysiologic studies to date, while

experimental and preliminary, have revealed differences in brain function for some athletes with suspected cumulative effects, those who are symptomatic, and those with residual brain dysfunction beyond that indicated by self-reported symptoms.

## NEUROPSYCHOLOGICAL OUTCOME

Many athletes with concussions have neurocognitive decrements as measured by traditional paper-pencil and computerized neuropsychological tests in the initial hours, days and potentially weeks post injury (15, 16, 24, 30, 70–76). In terms of group data, it has become a fairly robust finding that athletes tend to recover in terms of perceived symptoms and neuropsychological test performance within 2–14 days (1, 14, 15, 24, 77, 78).

In an NCAA prospective cohort study (14), 1,631 football players from 15 colleges completed preseason baseline testing during the 3 year study. Players with concussions ( $n = 94$ ) and noninjured controls ( $n = 56$ ) underwent assessment of symptoms, cognitive functioning, and postural stability immediately, 3 hours, and 1, 2, 3, 5, 7, and 90 days after injury. Concussed athletes' balance problems resolved within 3–5 days, self-reported postconcussion symptoms gradually resolved by day 7, and neurocognitive functioning improved within 5–7 days. By seven days post injury, 91% of athletes returned to personal baseline levels of symptom reporting.

Collins, Lovell, and Iverson recently have analyzed the results from a three-year, prospective, naturalistic, cohort study of high school football players. Participants were 2,141 high school athletes from Western Pennsylvania. During this 3-year study, 136 concussions were recorded and these athletes were carefully followed, clinically, until they were cleared to return to competition. The recovery rates were as follows: 1 week = 45%, 2 weeks = 73%, 3 weeks = 82%, 4 weeks = 91%, and 5 weeks = 97%. Thus, individual variability exists with recovery from sports concussion, especially in high school athletes, and the duration of symptoms can persist well beyond two weeks post injury.

Results from a six-year, prospective, National Football League concussion study have been published in a series of eight articles (9, 28, 78–83). A total of 887 concussions were recorded in 650 players during the study period. The time taken to return to play was as follows: (1) day of injury = 56.0%, (2) 1–6 days = 35.9%, (3) 7–14 days = 6.5%, and (4) more than 14 days = 1.6% (28). Those athletes who returned to play in the same game had fewer and briefer signs and symptoms of concussion, and they did not appear to have significantly increased risk for a second injury either in the same game or during the season (83).

A subset of concussed NFL players underwent baseline neuropsychological evaluations and then completed

a second evaluation ( $N = 95$ ) within a few days following their concussion ( $M = 1.4$  days,  $SD = 1.3$ ; (79)). The players did not show a single statistically significant decrement on any neuropsychological test when seen in the first few days post injury. These results, of course, are inconsistent with studies in both collegiate and high school athletes, where neurocognitive decrements are more pronounced. These results might reflect a selection bias (NFL athletes exhibit more rapid recovery, perhaps due to genetics/biological hardiness), or that age, and developmental factors may play a role in recovery from concussion. In fact, results from a recent study suggested that high school athletes might have slower recovery from concussive injury when compared to a matched collegiate sample (84).

In regards to cumulative effects, NFL athletes with a history of three or more concussions did not perform more poorly on neuropsychological testing than those with fewer than three (78). This finding, too, appears somewhat inconsistent with studies involving amateur athletes. Researchers have reported that three or more concussions in high school and university athletes are associated with small but measurable cumulative effects (34, 68, 85), and increased risk for future concussions (86, 87).

### CUMULATIVE EFFECTS

Athletes, their families, coaches, athletic trainers, and sports medicine professionals are concerned about possible lingering effects, or permanent brain damage, resulting from multiple concussions. The literature on cumulative effects will be reviewed in detail in this section. When considering repeated subconcussive and concussive blows to the head, the most obvious athlete group to study is boxers. Few would debate that a *career* in boxing can result in obvious changes to the structure and function of the brain (38, 88–92). However, this may not be the case with amateur boxers. Professional boxing differs from amateur boxing in a number of ways: amateur boxers are typically not the elite in their weight-class, use headgear and larger gloves, and have fewer rounds per fight. Therefore, it is not surprising to observe differences between amateur and professional boxers, for example, on measures such as whole brain regional cerebral blood flow (rCBF) (51, 52).

Taken as a whole, studies on *amateur* boxers have offered mixed results regarding changes in brain structure and function. Significant changes in cerebral perfusion have been reported in amateur boxers compared to non-boxing athletic controls (53). On the other hand, a series of studies by Haglund and colleagues that compared high and low match amateur boxers versus athlete and non-athlete controls reported no differences on a mini-mental status

examination or platelet MAO activity (93), magnetic resonance imaging (MRI) or computed tomography (CT) (42), neuropsychologic testing (64), or auditory evoked or event-related potentials, with only slight or moderate electroencephalographic (EEG) deviations between high match boxers and athletic controls (94). Similarly, Porter (95) observed no statistical change in a group of 19 amateur boxers over a period of nine years using neuropsychologic testing compared to non-boxing athletic controls.<sup>1</sup>

The literature on subconcussive blows to the head in other sports is also mixed. Some studies reported neuropsychological decrements (75) or temporary adverse effects immediately following repeatedly heading a soccer ball during practice (96). Other studies such as those associated with heading the soccer ball, tournament boxing,<sup>2</sup> or springboard diving generally suggest no statistically significant neuropsychological (6, 97–100) or balance effects (101).

Although the evidence regarding subconcussive effects is somewhat unclear, there is some evidence that a history of three or more concussions is associated with changes in cognitive neurophysiology (68), subjective symptoms (68, 102), and neuropsychological test performance (102). Furthermore, athletes with three or more concussions may be at increased risk of sustaining a future concussion (86), have worse on-field presentations of their next concussion (85), are more likely to have slowed recovery (86), and have greater acute changes in memory performance (102).

The literature regarding the persistent effects of two previous concussions is mixed. In regards to possible long-term effects, some researchers have reported significant findings (16, 103), others have not (68), and others reported equivocal results (e.g., 104). Further, no differences were observed on neuropsychological testing or symptom reporting for those with one versus two concussions (105). In a large-scale study, athletes with one or two previous concussions did not differ on neuropsychological testing or symptom reporting from athletes with no previous concussion on baseline, preseason testing (106). There is, however, preliminary evidence that athletes with two previous concussions have slower recovery times (86).

The studies indicating little or no change associated with subconcussive effects in boxers should be considered preliminary because they examine change over a short time frame (up to nine years) and do not take into account the possibility of long-term effects. This is important

<sup>1</sup> Sixty-six percent of the controls in this study were involved in some form of football with 28% reporting concussions.

<sup>2</sup> The study on boxers did not include those whose bout was stopped by the referee or those with epitaxis; boxers in these groups had increased simplex and choice reaction times compared to controls.

because the symptoms associated with chronic traumatic encephalopathy in boxers often show up later in life (107, 108). Similarly, the findings to date on three or more concussions should be considered preliminary – much additional research is needed because the aforementioned studies all have significant limitations in terms of methodology, generalizability, or both.

### Pathophysiology of Cumulative Effects

Given that there is general agreement regarding the existence of some form of cumulative effects in some athletes, the question can be asked: What is the pathophysiologic basis of these injuries? Specifically, are the changes based in the functioning of previously injured neurons, genetic differences related to the susceptibility to cumulative effects, or some other form of measurable permanent change?

Researchers have reported that axons of cultured human neurons have a remarkable capacity for stretch with no primary axotomy observed with strains below 65% of the length of the axon. In addition, axons exhibit the behavior of “delayed elasticity”. In other words, stretch causes a temporary deformation that gradually returns to the original orientation and morphology even though internal axonal damage was sustained (109). Once stretched, a pathophysiologic process begins that can lead to further structural change and metabolic dysfunction. First, strain on the axonal membrane causes an abnormal influx of  $\text{Na}^+$  through mechanosensitive sodium channels, a reversal of the  $\text{Na}^+$ - $\text{Ca}^{2+}$  exchangers, and activation of voltage gated  $\text{Ca}^{2+}$  channels (110). This in turn causes selective proteolysis or a breakdown of  $\text{Na}^+$  channels and progressively increasing levels of intra-axonal  $\text{Ca}^{2+}$  (111). It is the massive influx of  $\text{Ca}^{2+}$  that leads to damage to the axonal cytoskeleton and initiates the formation of axonal swellings.

Using an animal optic nerve stretch model, it was determined that stretch below four mm did not cause any morphological change in axons, a stretch of five mm produced changes in visual evoked potentials that were significantly different from controls, with six mm stretch causing morphological change including retraction balls and axonal swellings (112). Therefore, there appears to be a progression following a single injury from no apparent change in structure or function, to functional change, to structural change in the axon based on the extent of stretch. However, researchers have reported that repetitive mild injuries using similar or *lower* levels of force than those used to produce single mild injuries caused a greater number of structural and functional changes. For example, when comparing animals that received two mild injuries (using lower levels of force) to those that sustained a single mild injury, the number of foci with injured axons in the frontal lobes was significantly

greater in the two injury group (113). In another study, two consecutive mild brain injuries three days apart produced a similar biochemical pattern as found in severe TBI while those separated by five days appeared as two distinct mild injuries (114). This study points out the possibility of a “critical window” where subsequent mild re-injury can lead to significant pathophysiological change. Further, repeated mild injuries have been shown to cause sublethal but significant biochemical markers of cellular injury and the production of neurites with a beaded and damaged appearance. In this study, it was noted that cells undergoing repeated injury resembled those that sustained a single injury produced with greater magnitudes of stretch (115).

Human studies on the pathophysiology of repeated mild injury are limited to case studies, usually in retired athletes with suspected permanent and significant brain damage (i.e., “chronic traumatic brain injury,” “dementia pugilistica,” or “punch-drunk syndrome”), a distinct clinical entity from Parkinsonism (116). Former athletes, usually boxers, with this serious condition often have slurred speech, ataxic gait, memory impairment, personality changes, and Parkinsonism. An autopsy on two boxers with repetitive brain injury related to participation in contact sport revealed neuronal cytoskeletal changes (117).

The preliminary evidence on cumulative effects has led some to ask whether athletes are at risk for developing dementia due to participation in their sport (118) and whether there is a genetic basis for cumulative effects (89)? These questions have evolved mostly from the sport of boxing. One of the more comprehensive studies on this topic assessed brain damage in 30 boxers with varying age and experience. All three boxers who exhibited evidence of severe brain damage or dysfunction had at least one copy of the APOE  $\epsilon 4$  allele. This is compared with 50% of those with moderate damage, 25% of those with mild damage, and 18% of those with normal examinations. In addition, it was reported that there may be neuroprotective features associated with having the APOE  $\epsilon 2$  allele (107). Kutner and colleagues reported that as a group, older players who had the APOE  $\epsilon 4$  allele performed worse on cognitive testing than did all other players including those of the same age and younger players with the APOE  $\epsilon 4$  allele (119).

Beyond studies on the genetic make-up of athletes, there is preliminary evidence that neuronal DNA itself can be altered following mild injuries in animals. Following MTBI in rats, cells with condensed nuclei, chromatin, and shrunken and round cell bodies were observed. On occasion these cells contained what appeared to be apoptotic cell bodies (120). Regarding cumulative effects, increased vulnerability of stretched neurons to a secondary insult (e.g., physical or biochemical) was associated with the production of reactive oxygen species (ROS) that were

produced even when the stretch was sub-lethal. For example, the combination of mitochondrial ROS (superoxide) and nitric oxide (NO) into peroxynitrite leads to protein nitration, DNA degradation, and cell death. The DNA fragmentation seen in these cells was not considered apoptotic but was attributable to damage by reactive nitrogen species (121).

### Second Impact Syndrome

Second impact syndrome is related to an *extraordinarily rare* cascade of events in which an athlete experiences a catastrophic brain injury following a seemingly mild concussion. In theory, sustaining a second brain injury during a period of increased vulnerability with unresolved metabolic dysfunction has been linked to second impact syndrome. The pathophysiologic basis for second impact syndrome is thought to be cerebrovascular congestion or a loss of cerebrovascular autoregulation leading to considerable brain swelling and edema (122, 123). It has been reported that relatively few athletes, approximately 35 or more in the years between 1980 and 1993, have succumbed to this syndrome (122). When it occurs, morbidity is 100% and mortality is reported to occur in up to 50% of cases (122). To date, most cases of second impact syndrome have been reported in children (e.g., 124) or adolescents (125, 126). Recent animal modeling has indicated that a single mTBI revealed transient and minimal impairment on a composite neuroscore test and minimal breach of the blood brain barrier. If a second mild injury was inflicted within 24-hours of the first injury, a marked breakdown of the blood brain barrier occurred leading to swelling and edema (127). This change in blood brain barrier integrity following a second concussive injury occurring shortly after the first may be a possible mechanism for the rapid swelling and edema formation that occurs in humans.

### RECOVERY TIME AND RETURN TO PLAY DECISION-MAKING

Though significant individual variability exists in recovery from concussion, most group studies have indicated that a single concussion typically resolves in less than two weeks for most athletes (1, 14, 15, 24, 31, 77, 78). Current clinical experience and research has suggested that proper management of concussion should lead to a good prognosis in the vast majority of athletes. Most sports medicine researchers and professionals agree that returning an athlete to contact sport participation prior to complete recovery might increase the risk of poor outcome. Thus, the most important step a practitioner can take toward a positive prognosis is proper assessment and

management of concussion in the acute and follow-up stages of injury.

### Concussion Grading Scales

Traditionally, return to play decisions were based partially on concussion grading scales that served to classify individual injuries according to severity and offer return to play guidelines. During the past thirty years, over twenty concussion management guidelines have been published with the intent of providing guidance and direction for the sports-medicine practitioner in making complex return to play decisions. The authors of each of these guidelines also provided an accompanying grading scale designed to reflect and characterize the severity of the injury. Although these guidelines have very likely resulted in improved care of the athlete, these multiple directives also created significant confusion and sparked almost continuous debate. A historical review of all past and current concussion guidelines is beyond the scope of this chapter, however, brief review of four of the more popular guidelines is provided in Table 24-3.

Cantu originally proposed his grading scale and management guidelines based on clinical experience (128). However, Cantu was careful to emphasize that these guidelines were intended to supplement rather than replace clinical judgment. The original Cantu guidelines allowed return to play the day of injury if the athlete was symptom free both at rest and following physical exertion. For athletes who experienced any loss of consciousness (e.g., grade 3 concussion), a restriction of contact for one month was recommended. Athletes who had suffered a Grade 2 concussion were allowed to return to play in two weeks, if asymptomatic for a period of 7 days.

The Colorado Guidelines (125) were published in 1991 following the death of a high school athlete due to presumed Second Impact Syndrome and were drafted under the auspices of the Colorado Medical Society. These guidelines allowed for same day return to play if symptoms cleared within 20 minutes of injury. For Grade 3 concussion, these guidelines recommended immediate transport to a hospital for further evaluation. These guidelines were later revised under the sponsorship of the American Academy of Neurology (18). The AAN guidelines allowed return to competition the same day of injury if the athlete's signs and symptoms cleared within 15 minutes of injury. Grade 2 concussion was managed in a manner similar to the Colorado Guidelines, with return to competition within one week, if asymptomatic.

More recently, Cantu has amended his guidelines to emphasize the duration of post-traumatic symptoms in grading the severity of the concussion and making return to play decisions (129). Grade 1 concussion was redefined by an absence of loss of consciousness, and post-concussion



**TABLE 24-3**  
**Recent Concussion Grading Scales**

GUIDELINE	GRADE 1	GRADE 2	GRADE 3
Cantu (133)	1. No loss of consciousness 2. Posttraumatic amnesia last less than 30 minutes	1. Loss of consciousness lasts longer than 5 minutes OR 2. Posttraumatic amnesia lasts longer than 30 minutes	1. Loss of consciousness lasts longer than 5 minutes OR 2. Posttraumatic amnesia lasts longer than 24 hours
Colorado (125)	1. Confusion without amnesia 2. No loss of consciousness	1. Confusion with amnesia 2. No loss of consciousness	1. Loss of consciousness (of any duration)
AAN (18)	1. Transient confusion 2. No loss of consciousness 3. Concussion symptoms mental status changes resolve in less than 5 minutes	1. Transient confusion 2. No loss of consciousness 3. Concussion symptoms or mental status change lasts longer than 15 minutes	1. Loss of consciousness (brief or prolonged)
Cantu (129)	1. No loss of consciousness  OR 2. Posttraumatic amnesia or signs/symptoms lasts longer than 30 minutes	1. Loss of consciousness lasts less than 1 minute  OR 2. Posttraumatic amnesia lasts longer than 30 minutes but less than 24 hours	1. Loss of consciousness lasts more than 1 minute  OR 2. Posttraumatic amnesia lasts longer than 24 hours OR 3. Post-concussion signs or symptoms last longer than 7 days

signs or symptoms lasting less than 30 minutes. Same day return to competition was allowed only if the athlete was completely asymptomatic following the injury.

The above mentioned management guidelines reached their peak popularity during the 1980's and 1990's. However, in the late 1990's, sports medicine practitioners and organizations began to question the scientific basis of these guidelines (130). This trend prompted the American Orthopaedic Society for Sports Medicine (AOSSM) to sponsor a workshop with the purpose of re-evaluating current guidelines and establishing practical alternatives (131). Although the AOSSM guidelines did not differ substantially from prior guidelines, this workshop started a trend away from the use of a numeric grading systems for determination of return to play following concussion (e.g., as developed by the Cantu, Colorado, and AAN guidelines). The AOSSM guidelines stressed more individualized management of injury, rather than applying general standards and protocols.

### Current Return to Play Criteria

Currently, prevailing standards of care require an athlete to satisfy three conditions before returning to play. From the perspective of a sports medicine physician, the athlete should be asymptomatic at rest and during non-contact

exertion before return to play is indicated. Once asymptomatic at rest, the athlete is then progressed through increasing non-contact physical exertion, until he/she has demonstrated asymptomatic status with heavy non-contact physical exertion and non-contact sport-specific training. In addition, the athlete should demonstrate full recovery of cognitive function exhibited by his/her performance on a neuropsychological testing battery (if available).

### Asymptomatic Status at Rest

Separately or in conjunction with administration of a neurocognitive test battery, the athlete should complete a symptom inventory (such as the Postconcussion Scale, see Table 24-4) or symptom interview both on the sideline (may be brief) and serially throughout recovery. Before progressing to any significant level of physical exertion, the athlete should report being asymptomatic at rest for at least 24 hours. If the athlete's report of asymptomatic status is suspected to be false, a careful discussion of the importance of reporting all symptoms should be initiated with the athlete. If there are others who present for evaluation with the athlete (e.g., parents, athletic trainers, or teammates), asking these third party informants about the athlete's previous or current symptom complaints might be helpful.

**TABLE 24-4**  
**Post-Concussion Scale**

RATE YOUR SYMPTOMS OVER THE PAST 2 DAYS

SYMPTOM	NONE	MILD	MODERATE	SEVERE			
Headache	0	1	2	3	4	5	6
Nausea	0	1	2	3	4	5	6
Vomiting	0	1	2	3	4	5	6
Balance problems	0	1	2	3	4	5	6
Dizziness	0	1	2	3	4	5	6
Fatigue	0	1	2	3	4	5	6
Trouble falling asleep	0	1	2	3	4	5	6
Sleeping more than usual	0	1	2	3	4	5	6
Sleeping less than usual	0	1	2	3	4	5	6
Drowsiness	0	1	2	3	4	5	6
Sensitivity to light	0	1	2	3	4	5	6
Sensitivity to noise	0	1	2	3	4	5	6
Irritability	0	1	2	3	4	5	6
Sadness	0	1	2	3	4	5	6
Nervousness	0	1	2	3	4	5	6
Feeling more emotional	0	1	2	3	4	5	6
Numbness or tingling	0	1	2	3	4	5	6
Feeling slowed down	0	1	2	3	4	5	6
Feeling mentally "foggy"	0	1	2	3	4	5	6
Difficulty concentrating	0	1	2	3	4	5	6
Difficulty remembering	0	1	2	3	4	5	6
Visual problems	0	1	2	3	4	5	6

### Asymptomatic Status with Physical Exertion

Once an athlete demonstrates asymptomatic status at rest, he or she should begin a graduated return to physical exertion prior to contact participation, because post-concussion difficulties might evolve with increased cerebral blood flow. The Vienna group and the Prague group have encouraged a graduated protocol (19, 132). Briefly, the protocol involves an athlete successfully moving through the following exertional steps in 24-hour periods: (1) light aerobic exercise (walking, stationary biking), (2) sport-specific training (ice skating in hockey, running in soccer- typically moderately exertional), and (3) non-contact training drills (usually heavily exertional). If the athlete's previously resolved post-concussion symptoms return at any point during the graded return to physical exertion, the athlete should return to the previous exertion level at which they were last asymptomatic.

### Intact Neurocognitive Function (either compared to baseline or normative data)

Neurocognitive recovery can be considered achieved when the athlete's performance either returns to baseline levels or, in the absence of baseline, is consistent with premorbid

estimates of functioning when the test data are compared to normative values (clinicians should utilize test batteries that have readily available athlete-specific norms).

Pre-season or baseline neuropsychological assessment can be very helpful for comparing post-injury functioning to "normal" functioning for the injured athlete. Some practitioners prefer to complete serial follow-up using computerized neuropsychological testing in order to gain insight into the extent and type of cognitive impairment created by the injury. The first test is often performed while the athlete remains symptomatic, then completed again once the athlete is asymptomatic to gauge progress and ensure a return to baseline or premorbid expectations of cognitive functioning. Other practitioners prefer to test the athlete when he/she is asymptomatic at rest and with heavy non-contact exertion, and prior to returning the athlete to any type of contact participation. This may maximize the chances that neuropsychological testing will only need to be performed once at follow-up.

Once the athlete is symptom free at rest and with physical exertion, as well as within expected levels on cognitive testing (if available), he/she may return to full-contact training, then to competition. Again, if any symptoms emerge with return to contact participation, the athlete should return to non-contact physical exertion.

## CONCLUSIONS

This chapter was intended to be a comprehensive overview of concussion in sport, dealing with topics such as definitions, on-field/sideline presentation, pathophysiology, structural and functional imaging, neuropsychological outcome, cumulative effects, and return to play decision making. The pathophysiology of concussion has been conceptualized as a multilayered neurometabolic cascade (e.g., 22). The primary mechanisms include ionic shifts, abnormal energy metabolism, diminished cerebral blood flow, and impaired neurotransmission. Fortunately, the brain undergoes a dynamic restorative process in the initial days to weeks following a concussion. From a commonsense perspective, the ionic shifts, abnormal energy metabolism, diminished cerebral blood flow, and impaired neurotransmission believed to be associated with concussions in sports reinforces the importance of immediate rest following injury. Although not established empirically, it seems reasonable to assume that vigorous exercise or hard physical contact might exacerbate the pathophysiology described above.

Many athletes with concussions have neurocognitive decrements as measured by traditional paper-pencil and computerized neuropsychological tests in the initial hours, days, and potentially weeks post injury. In terms of group data, it has become a fairly robust finding that athletes tend to recover in terms of perceived symptoms and neuropsychological test performance within 2–14 days. However, individual variability exists in recovery rates, especially in high school athletes, and the duration of symptoms can persist well beyond two weeks post injury.

Researchers have reported that three or more concussions in high school and university athletes are associated with small but measurable cumulative effects, and increased risk for future concussions. The literature on subconcussive blows to the head, or the long-term effects of one or two previous concussions, is mixed. In general, there is insufficient evidence at this time to conclude that subconcussive blows or 1–2 previous concussions results in adverse long-term effects in the average athlete.

Ideally, athletes should satisfy three conditions before returning to play. The athlete should be asymptomatic at rest and during non-contact exertion. Once asymptomatic at rest, the athlete is then progressed through increasing non-contact physical exertion, until he/she has demonstrated asymptomatic status with heavy non-contact physical exertion and non-contact sport-specific training. In addition, the athlete should demonstrate full recovery of neurocognitive function exhibited by his/her performance on a neuropsychological testing battery (if available).

The management of sports-related concussion has evolved rapidly over the past decade and has been based on an explosion of laboratory and clinical research.

Current prevailing models of assessing readiness for return to play following injury have been increasingly based on research studies rather than on panels of experts, which represented the zeitgeist in the 1980's and 1990's. Contemporary models of care have recognized the complexity of the recovery process following concussion and are beginning to consider the unique contribution of factors such as the athlete's age, developmental history, and past injury status in determining outcome. This recognition of the interplay between multiple variables is leading to the development of a much more sophisticated understanding of the recovery process; we anticipate that this will continue in the near future. Given the current trend towards research-based models of clinical care, we anticipate that concussion management will continue to grow and develop as our capacity for completing large-scale clinical research projects increases and we are able to meld this information with other advances in the neurosciences such as structural and functional neuroimaging and electrophysiological techniques.

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# 25

## Assessment and Rehabilitative Management of Individuals with Disorders of Consciousness

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**T**here has been a resurgence of interest and scientific inquiry concerning disorders of consciousness (DOC) over the last decade. American and

European initiatives have led to the development of guidelines for assessment, prognosis and rehabilitation of individuals in coma and the vegetative state (VS) (1–3) and have contributed to the formulation of neurobehavioral criteria for the minimally conscious state (MCS) (4). These initiatives, coupled with the development of improved behavioral and neuroimaging assessment procedures, have fostered increasing consensus regarding conceptual and empirical approaches to understanding DOC.

This chapter will review and critique the major developments in this area that have influenced the clinical management of DOC. Following a review of the diagnostic criteria associated with coma, VS and MCS, new insights garnered from functional neuroimaging studies into the pathophysiology of these disorders will be discussed. Behavioral and radiologic assessment techniques developed specifically for this population will be discussed in relation to diagnostic and prognostic utility. Medical, environmental and neuromodulatory interventions designed to facilitate recovery of cognition will be reviewed and discussed relative to efficacy. Clinical predictors of outcome will be outlined, with particular attention to differences

between individuals diagnosed with VS and MCS and general recommendations for clinical management will be outlined. Finally, ethical issues will be defined and future directions for research proposed.

### DEFINITIONS AND DIAGNOSTIC CRITERIA

Numerous terms have been offered to characterize states of altered consciousness, many of which have not been operationalized (see table 25-1). Not surprisingly, estimates of misdiagnosis among disorders of consciousness range from 15% to 43% (5–7). In recognition of this problem, a multi-disciplinary group was assembled in 1995 through the auspices of the Aspen Neurobehavioral Conference to formulate a consensus statement regarding the diagnostic and prognostic criteria for coma, VS and MCS. The recommendations of the Aspen Group were subsequently endorsed by the American Academy of Physical Medicine and Rehabilitation, the American Association of Neurologic Surgeons, the American Congress of Rehabilitation Medicine, the Brain Injury Association of America, and the Child Neurology Society. The definition and diagnostic criteria for MCS, crafted by the Aspen Group, was published in 2002 in *Neurology*, the official journal of the American Academy of Neurology (4).



TABLE 25-1

**Terms Used to Refer to Disorders of Consciousness**

Akinetic mutism	Minimally responsive state
Apallic syndrome	Permanent vegetative state
Coma	Persistent vegetative state
Coma vigil	Post coma unawareness
Cognitive death	Prolonged coma
Decerebrate state	Prolonged post-traumatic unconsciousness
Low level	Vegetative state
Minimally conscious state	

**Coma**

Coma is a state of pathologic unconsciousness in which the eyes remain closed and the patient cannot be aroused (8). It is most often the result of severe, diffuse bi-hemispheric lesions of the cortex or underlying white matter, bilateral thalamic damage or paramedian tegmental lesions. The clinical criteria for diagnosing coma were described by Plum and Posner in 1982 (9) and remain well accepted. The defining feature of coma is the complete loss of spontaneous or stimulus-induced arousal. The eyes remain continuously closed despite the application of noxious stimuli and there are no sleep/wake cycles on EEG. On examination, there is no evidence of purposeful motor activity, no response to command and no indication of receptive or expressive language ability. Coma is a self-limiting state that typically resolves within two to four weeks in those who survive the initial injury.

**Vegetative State (VS)**

The vegetative state has been mired in controversy since it was first introduced by Jennett and Plum (10) more than 30 years ago. The term itself is controversial because it is considered to be pejorative by the lay public, and because clinicians have not been able to agree on the prognostic parameters associated with this diagnosis. VS is a condition in which awareness of self and environment is presumed to be absent and there is an inability to interact with others, although the capacity for spontaneous or stimulus-induced arousal is preserved (11). VS typically follows a period of coma but may also arise from developmental malformations or may represent the culmination of progressive degenerative or metabolic disorders. The neuropathologic substrate is usually determined by the cause of injury. Diffuse axonal injury is the most common finding in post-traumatic VS. Vascular causes of VS are often associated with paramedian thalamic damage and diffuse laminar cortical necrosis is frequently noted following anoxic brain injury. The diagnosis of VS is made when there is no evidence of sustained or reproducible, purposeful behavioral responses to visual, auditory, tactile or

noxious stimuli, and no evidence of language comprehension or expression. Unlike coma, intermittent periods of wakefulness (i.e. eye opening) occur in VS and represent functional restoration of the reticular system.

The term *persistent VS* (PVS) remains controversial, in part, because it has been used inconsistently in the medical literature. The most current practice parameter on PVS published in 1995 by the American Academy of Neurology (1) stipulates that PVS can be diagnosed after one month following either traumatic or non-traumatic brain injury. After reviewing the published literature on PVS, the AAN introduced a new term, *permanent VS*, suggesting that this term be applied three months after non-traumatic brain injury, and after twelve months following traumatic injury. The distinction between persistent and permanent VS is intended to establish the point after which recovery of consciousness is highly improbable.

According to the AAN practice parameter, PVS is a diagnostic term and does not imply irreversibility. In view of the inconsistent application of PVS and the high rate of recovery of consciousness that occurs between three and twelve months post-injury in individuals who remain in VS longer than one month (12, 13), the Aspen Group recommended that the term PVS be abandoned. Instead, they proposed that when the diagnosis of VS is made, it should routinely be accompanied by a description of the injury and the length of time since onset as both of these factors provide prognostic information (14).

**Minimally Conscious State (MCS)**

MCS is a condition of severely altered consciousness in which there is minimal but definite behavioral evidence of self or environmental awareness (4). MCS usually represents a transitional state reflecting improvement in consciousness from coma or VS, or progressive decline as in neurodegenerative disease (e.g., Alzheimer's disease). The natural history and long term outcome have not been fully characterized, however, at least ten papers have been published on MCS since this condition was defined in 2002. The neuropathologic substrate of post-traumatic MCS was recently investigated in a post-mortem analysis completed by Jennett and colleagues (15) who found that the typical lesion profile consists of grade 2 or 3 diffuse axonal injury with multi-focal cortical contusions, sometimes accompanied by thalamic involvement. In comparison to patients diagnosed with VS, thalamic lesions were notably less prevalent in MCS (50%) relative to VS (80%). Based on these findings, MCS appears to be characterized by greater sparing of cortico-thalamic connections which may account for why patients in MCS retain some capacity for cognitive processing.

The diagnosis of MCS is based on clearly discernible evidence of one or more of the following behaviors: 1) simple command-following, 2) intelligible verbalization,

3) recognizable verbal or gestural “yes/no” responses (without regard to accuracy) or 4) movements or emotional responses that are triggered by relevant environmental stimuli and cannot be attributed to reflexive activity. Examples of the fourth criterion include a) smiling or crying following exposure to emotional (e.g., family photographs) but not neutral stimuli (e.g., photographs of objects), b) vocalizations or gestures that occur in direct response to specific linguistic prompts, c) accurate reaching toward objects placed within the immediate visual field, d) manipulation of objects placed in the hand and e) sustained visual fixation or pursuit eye movements.

In making the diagnosis of MCS, it is important to consider the frequency and complexity of the behavior observed. When there is evidence of rudimentary cognition only (e.g., inconsistent visual tracking), the diagnosis of MCS requires serial reassessment. At the opposite end of the MCS spectrum, patients who demonstrate consistent evidence of complex cognitively-mediated behavior (e.g., command following) fall at the upper limit of MCS.

Within the diagnostic category of MCS, there is a subgroup of patients whose behavior is difficult to characterize, both from a practical as well as theoretical standpoint. Some MCS patients infrequently initiate behavior or respond to environmental prompts, but on occasion, exhibit behaviors that infer complex cognitive processing (e.g., follow countermanding or go-no go commands). It is not unusual for these individuals to show marked fluctuations in behavioral responsiveness across examinations. We recently evaluated an individual who was able to provide reliable responses to a series of yes/no questions during the initial examination. On follow up examination conducted 24 hours later, responses to the same questions were inconsistent and unreliable. There is little agreement as to whether patients who infrequently engage in complex responses should be included in the MCS category. It is often difficult to determine whether the low rate of behavioral responsiveness observed in these individuals is primarily due to sensory limitations, motor dysfunction, abulia or fluctuations in level of consciousness.

### Emergence from MCS

Emergence from MCS is signaled by the recovery of interactive communication or functional object use. In contradistinction to MCS, emergence from MCS requires *reliable and consistent* evidence of either communication or object use. Communication may occur through verbal responses, gestural means or augmentative devices. “Functional object use” requires discrimination among items presented (e.g., comb brought to head and toothbrush to mouth). Aphasia and apraxia must be ruled out as contributing or causative factors in patients who don’t meet the criteria for reliable communication ability or functional object use.

The last ten years have witnessed movement toward achieving universally agreed upon terminology for disorders of consciousness. This is an essential step in assuring accurate diagnosis and promoting well-informed treatment decisions. Unless there is a common frame of reference to guide research and clinical practice, the difficulties inherent in evaluating and treating disorders of consciousness will prove insurmountable.

## PATHOPHYSIOLOGY AND NEUROIMAGING

### Neuropathology of VS and MCS

Traumatic and non-traumatic VS have distinct and identifiable pathologies. Adams et al. (16) studied 49 patients remaining in VS for at least one month until death and found that non-traumatic injuries included severe bilateral thalamic damage in all instances and, in the majority of cases, were associated with diffuse cortical damage. In contrast, traumatic etiologies associated with VS showed grade 2 and 3 diffuse axonal injuries and severe thalamic degeneration in almost all of patients who survived for 3 months before death. These pathological studies confirm the intuition that the chronic vegetative state is characterized by overwhelming cerebral damage. An important conclusion that is often overlooked is that the most consistent and severe pathologies arising from both types of injuries are in subcortical structures, particularly the thalamus. The cerebral cortex is generally spared in traumatic VS, with only about 10% of patients showing diffuse ischemic neocortical injury patterns; brainstem damage is uncommon in chronic VS patients emphasizing that VS is primarily a disorder of cerebral integration at the thalamocortical level.

No comprehensive study has evaluated specific anatomic pathologies associated with MCS. Jennett and colleagues (17) reported 65 autopsies of patients with traumatic brain injury leading either to VS or severe disability and found wide variation in underlying neuroanatomical substrates. This study included 12 patients with histories consistent with MCS at the time of death. Of note, two of the MCS patients demonstrated only focal brain injuries, without DAI or focal thalamic infarction (a consistent finding in approximately half of the severely disabled patients). Further work to determine the pathological correlates of MCS is required.

### Functional Neuroimaging Studies

Several new brain imaging techniques are providing important insight into the mechanisms of neurological disorders of consciousness. Functional MRI (fMRI) and functional positron emission tomography ( $^{15}\text{O}$ -PET) studies respectively correlate changes in blood oxygen level and cerebral blood flow with neuronal activation.

Precise correlational studies of single-unit and multi-unit neuronal recordings from brain regions simultaneously studied using fMRI techniques indicate that fMRI signal activations are tightly correlated with neuronal population activity (18). These findings support the use of both fMRI and  $^{15}\text{O}$ -PET activations as a proxy for neuronal activation *per se*. Brain metabolism can also be quantified in neuroimaging studies using fluorodeoxyglucose positron emission tomography (FDG-PET) imaging, a measure of cerebral glucose metabolic rates. FDG-PET studies in patients with Parkinson's disease have correlated regional glucose metabolism with neuronal firing rates in cerebral structures (19). Direct measurements of cerebral metabolism and neuronal activity demonstrate a rough equivalence of metabolic rate and mean firing rate of population of neurons (20). Combined with traditional structural MRI imaging and EEG (or magnetoencephalography, MEG, recordings obtained from measurements of the brain magnetic field) these techniques offer an integrative view of the damaged brain.

*Pet Studies* The clinical judgment of unconsciousness in PVS was first supported in imaging studies by fluorodeoxyglucose positron emission tomography (FDG-PET) studies that revealed overall cerebral metabolism to be reduced by 50% or more below normal levels in PVS patients (21–24). More recently, Schiff and colleagues used functional brain imaging techniques including fluoro-deoxyglucose-positron-emission tomography (FDG-PET), magnetoencephalography (MEG) and magnetic resonance imaging (MRI) were combined with clinical assessments (25, 26). These studies identified novel evidence of the modular organization of brain systems in three patients who retained small islands of cerebral metabolic activity that correlated with clinically identified behavioral fragments. In one case, a 42 year old male diagnosed with post-traumatic VS of seven years duration, repeatedly displayed selective emotional responses following exposure to specific environmental events. He exhibited pronounced eye and mouth-opening, pupillary dilatation and groaning when touched or presented with loud noise, giving the appearance of grave distress. Conversely, when exposed to soft music or his mother's soothing voice, he showed signs of sympathetic and behavioral relaxation. PET data indicated that the patient's global resting metabolic rate was approximately 30% of normal, however, the right putamen, caudate, orbitofrontal cortex, lateral and superior temporal cortex showed elevated metabolism up to nearly 50% of normal levels. When correlated with the behavioral findings, the PET results appeared to reflect partial preservation of the neural network responsible for receptive prosody.

Several investigators have employed  $^{15}\text{O}$ -PET imaging techniques to the evaluate PVS patients. Laureys and colleagues have identified a marked loss of distributed

network processing in the vegetative state (27–29). In their studies, elementary auditory and somatosensory stimuli were presented to PVS patients and normal control subjects and compared to baseline resting conditions in  $^{15}\text{O}$ -PET subtraction paradigms; PVS patients demonstrated a loss of brain activations outside of primary sensory cortices for both types of stimuli. Cortical regions identified as 'hierarchically higher-order' multi-modal association areas active in the normal control subjects did not activate in the PVS patients. Laureys et al.'s findings are consistent with evidence of early sensory processing in PVS patients as measured by evoked potential studies and add important additional information about the integrity of cerebral information processing in PVS. Menon and colleagues (30) described a 26 year old woman in a persistent vegetative state (PVS) four months following an attack of acute disseminated encephalomyelitis that functionally impaired both cortical and subcortical (brainstem and thalamic) structures. Right occipital-temporal regions in this patient demonstrated selective activation of the right fusiform gyrus and extrastriate visual association areas with visual stimulation. These results were obtained in response to presentation of familiar faces and scrambled images. No other evidence of cortical processing was reported but the patient became increasingly responsive at 6 months and minimally expressive at 8 months into the course of her illness. Menon et al. interpreted this activity measured at four months as indicating a recovery of minimal awareness. However, such selective identification of relatively complex information processing may not alone index recovery of cognitive function or even potential for recovery (25, 31).

Only a few studies have addressed patterns of brain activation in MCS patients. Boly et al. (32) used the same  $^{15}\text{O}$ -radiolabeled PET paradigms for auditory stimuli tested in PVS patients to examine responses in MCS compared to healthy control subjects. Both MCS and normal subjects showed activation of the bilateral superior temporal gyri (Brodmann areas 41, 42 and 22) compared to earlier studies in the PVS patients where activation was limited to bilateral Brodmann areas 41 and 42 (33). Laureys et al. showed more widespread activation of  $^{15}\text{O}$ -radiolabeled PET responses for auditory stimuli with emotional valence (i.e., infant cries and patient's own name) than that for meaningless noise in an MCS patient (34).

*fMRI Studies* Schiff et al. (35) presented fMRI studies of two MCS patients, one related to TBI and the other to a spontaneous intracranial hemorrhage who remained in MCS for more than 18 months. When these patients were passively exposed to audiotaped narratives provided by family members, widespread activation of the language network was observed on fMRI. However, an important dissociation was observed in MCS patients compared to normal controls., When the narratives were time-reversed



so that the semantic content was no longer discernible, there was a marked reduction in the extent and magnitude of activation of language structures, unlike the normal controls who showed a slight increase in activation (see figure 25-1). For both patients studied, FDG-PET revealed marked reduction of resting metabolic rates to near VS levels. The low resting metabolic activity suggests that the MCS patients may suffer a severe deficit of ‘baseline’ brain activity proposed by Gusnard and colleagues (36) to account for high resting cerebral metabolic rates in the normal human brain. This suggests that patients in MCS may not be able to recruit “top-down” monitoring functions necessary for processing ambiguous or complex environmental information. It is important to note that although functional brain imaging may eventually provide useful correlates of the differences in MCS and PVS evident at the bedside, at present these studies cannot be used to advance diagnostic or prognostic distinctions.

Bekinschtein, Miklison, Sigman & Manes (37) recently reported evidence of emotion processing in an MCS patient who suffered a severe traumatic brain injury using functional magnetic resonance imaging (fMRI). When they played a recording of the patient’s mother’s

voice, functional MRI demonstrated activation of the amygdala and the insula, subcortical structures related to emotion. Functional connectivity between the secondary auditory cortex and temporal and prefrontal cortices suggested some potential for higher order integrative processes necessary for conscious auditory perception in MCS patients.

## CLINICAL ASSESSMENT

Prior to the last decade, procedures for evaluating individuals with disorders of consciousness were limited to the Glasgow Coma Scale (38) MRI and EEG studies. These procedures continue to be useful during the acute stage of recovery but represent relatively gross indicators of cerebral dysfunction. Specialized behavioral and neuroradiologic protocols have recently been developed in an attempt to provide a more specific means of monitoring recovery across the subacute and post-acute periods and to improve outcome prediction.

### Bedside Examination

There are no standardized evaluation procedures for the clinical bedside examination of patients with impaired consciousness. Most clinicians rely on systematic evaluations of arousal and behavioral responses to various forms of stimulation. Nevertheless, frequent errors in diagnosis occur, (5, 6) either because of a misinterpretation of responses or examinations that are inadequate to detect minimal, inconsistent responsiveness.

The bedside neurological examination of patients with impaired consciousness should focus on two general areas, assessment of the integrity of the central nervous system, particularly brainstem pathways (e.g. pupillary responses, ocular movements, oculovestibular reflexes, breathing patterns) and the presence of higher level cortical functions (e.g. purposeful, voluntary behaviors). The examiner’s task is to systematically elicit and distinguish behaviors that are reflexive or automatic, reliant on spinal or subcortical pathways, from those that are cortically-mediated and represent some level or awareness or purposeful intent.

Cognitive awareness or conscious intent may be difficult to interpret when responses are extremely inconsistent or simple. There is an inverse relationship between the dimensions of *complexity* and *consistency* when judging whether particular behaviors imply consciousness. When a behavior is more complex, such as a verbalization, fewer instances of the response are sufficient to demonstrate consciousness. When a behavior is less complex, such as a finger movement, more frequent occurrences are necessary to establish a link to stimulus awareness or conscious intention. For this reason, single bedside examinations are often inadequate to conclusively establish level of

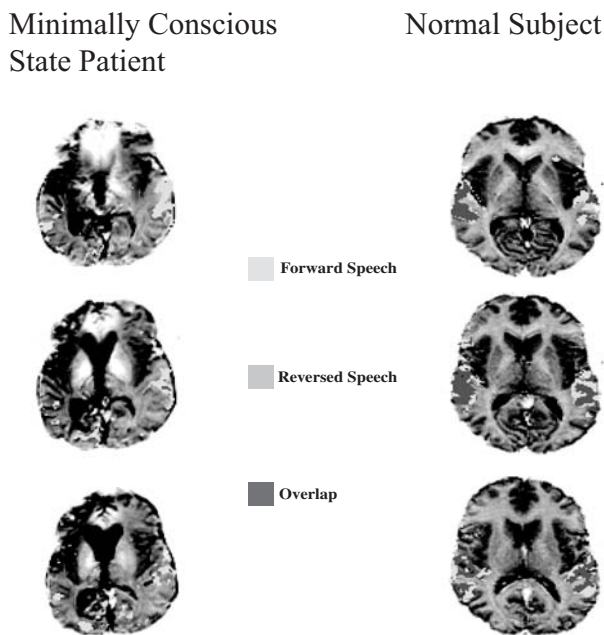


FIGURE 25-1

Images from fMRI studies of MCS patients and normal subjects. MCS patient shows widespread network activation for forward presentation of spoken narratives (yellow color), but time-reversed narratives produce only small regional activation of primary auditory cortex (red colored areas showing overlap for both stimulus types). In contrast, the normal subjects activate the entire network roughly equally for both stimulus conditions as seen in predominance of red colored regions for the normal subject

**TABLE 25-2**  
***A Systematic Approach to the Examination of Patients with Impaired Consciousness Includes the Following Steps***

1. Brainstem integrity and other subcortical evaluation
  - Pupillary response, blink reflex to visual threat
  - Ocular movements, gaze deviations
  - Oculovestibular reflexes (oculocephalic (“doll’s eyes”) maneuvers, calorics)
  - Corneal response
  - Gag reflex
  - Breathing pattern
  - Decerebrate postures
  - Other posturing, reflexes and tone
2. Cortical functioning
  - a. Observation of spontaneous activity
    - Purposeful, complex movements (involving cortically mediated isolated motor control) vs. posturing (decorticate or decerebrate) or reflex or stereotyped, patterned (subcortically mediated) movements
    - Spontaneous vocalizations or verbalizations
    - Eye movements (signs of fixation or tracking vs. nonspecific roving or no movement)
  - b. Responses to stimulation or environment
    - Tracking or fixation to stimuli (try salient stimuli such as familiar pictures, faces, mirror)
    - Verbal stimulation (e.g. patient’s name, commands, social greetings):  
 Begin with simple commands sampling a variety of areas under different neural control, favoring those areas of potentially preserved movement.
      - Eye commands – e.g. ‘look up’, ‘blink twice’;
      - Limb commands – e.g. ‘make a fist’, ‘show 2 fingers’, ‘raise your arm’;
      - Oral commands – e.g. ‘open mouth,’ ‘stick out tongue’;
      - Axial or whole body commands – e.g. ‘turn your head,’ ‘lean forward’).
      - Ask patient to ‘stop moving’ or ‘hold still’ to distinguish from spontaneous repetitive movements.
    - Noxious stimulation
      - Look for localization or purposeful defensive maneuvers vs. reflexive or generalized, stereotyped movements or facial expressions.
    - Response in contingent relationship to environment or other stimuli
      - Look for intentional reach for or manipulation of objects on or around the patient (e.g. pulling at tubes, clothing, items placed in the hand)
      - Look for changes in facial expression contingent on stimuli such as familiar voices, particular conversation, pictures, music, etc.
      - Look for attempts at purposeful mobility in bed, chair, and even ambulation
      - Gestural behaviors indicating tentative communication (e.g. yes/no signals)
    - Confounding factors affecting arousal (e.g., centrally acting medications, concurrent illness, subclinical seizures);
    - The potential influence of aphasia, apraxia and other higher cortical disorders that may affect ability to respond to commands.

unconsciousness. Repeated assessments and use of standardized evaluations (see below) may be necessary for diagnostic accuracy. Table 25-2 presents a systematic approach to the neurological examination of patients with impaired consciousness.

There are several common problems that can lead to inaccurate diagnosis of consciousness in patients with impaired consciousness. These include:

- Attributing purposeful intent for responses that are reflexive or generalized to any form of stimulation;
- Inadequate evaluation to detect conscious behavior – e.g. insufficient sampling time, inadequate arousal, inappropriate choice of stimuli;

- Over- or underconsideration of family or other’s observations of purposeful behavior (i.e., failure to recognize that family may be first to observe signs of consciousness or to overattribute purposeful intent);
- Simple, cortically mediated behaviors of uncertain cognitive significance; e.g. simple isolated limb movements;

The examiner should use strategies to account for some of these confounds and maximize the chance of detecting signs of conscious behavior. The clinician should:

1. *Assure optimal arousal.* There should be an adequate warm-up period, with verbal and tactile stimulation

to promote wakefulness. Deep pressure stimulation is often effective. Positioning is important and patients are usually more wakeful sitting up. The time of day, the patient's sleep-wake cycles and fatigue from activities preceding the neurological examination all have to be considered. Sedating medications should be avoided and treatable medical conditions should be addressed.

2. *Assure optimal environmental conditions.* Avoid distractions, provide adequate lighting, remove physical restrictions to movement and position stimuli to the patient's best advantage.
3. *Consider stimulus duration and rate.* Use a long enough presentation time and interstimulus interval to allow time for the patient to respond and to minimize perseveration. Recognize that as the interval between stimulus and response increases, the chance that a spurious response is mistakenly attributed to a stimulus also increases. Watch for signs of response fatigue.
4. *Avoid unnecessary complexity in command-following trials.* Use simple declarative language, one request at a time.
5. *Consider the patient's motor repertoire in choosing commands.* Use commands that incorporate motor responses that appear to be within the patient's capabilities, such as spontaneously observed movements.
6. *Distinguish purposeful from reflexive behavior.* When attempting to elicit movements to command, avoid responses that may represent common reflexive behaviors; e.g. squeeze hands, blink eyes.
7. *Evaluate a variety of potential responses and employ a range of different stimuli.* Attempt to elicit responses to a few different types of command – e.g. a limb command and an eye command. Look for other forms of purposeful behavior; e.g. manipulation of an object placed in the patient's hand; social handshake; purposeful resistance to unpleasant stimulation.
8. *Assure adequate examination time and perform serial reassessments.* Quick bedside evaluations, such as typical morning rounds, are often not adequate in detecting responses in patients with DOC. Repeated reassessments are necessary to establish response consistency, validity of examination findings and accuracy of the diagnosis.
9. *Pay attention to observations of others.* Families, nurses, therapists, who are more familiar or spend more time with the patient, often observe behaviors associated with consciousness before they are observed by the physician. The physician's assessment should incorporate these observations.

### Standardized Rating Scales

During the 1990's, advances in trauma care led to an increase in the number of survivors of severe brain injury.

Consequently, neurorehabilitation programs experienced an increase in the number of admissions involving patients with prolonged DOC. In light of these changes, neurorehabilitation specialists recognized the need for reliable assessment instruments that could detect subtle but potentially important clinical changes after the acute period of recovery. This resulted in a proliferation of standardized neurobehavioral assessment scales designed to gauge level of consciousness in unresponsive or poorly responsive patients. These instruments were intended to provide a comprehensive overview of neurobehavioral functions and, at the same time, to detect subtle changes in response frequency and complexity. The JFK Coma Recovery Scale (CRS) (39), the Western Neuro Sensory Stimulation Profile (WNSSP) (40), the Coma/Near Coma Scale (CNC) (41), the Sensory Modality Assessment Rehabilitation Technique (SMART) (42) and the Wessex Head Injury Matrix (43) represent examples of such measures. Although the validity and reliability of these instruments have been shown to be adequate (39–44), other important psychometric characteristics and their diagnostic and prognostic utility have not been well-studied.

The CRS was recently revised in an effort to improve differential diagnostic accuracy between VS and MCS (45). Interrater and test-retest reliability were found to be high for CRS-R total scores. Total scores were also significantly correlated with the Disability Rating Scale, providing evidence for concurrent validity. Analysis of internal consistency revealed moderate intercorrelations between the total CRS-R score and individual subscale scores suggesting that the scale is a reasonably homogeneous measure of neurobehavioral function. There was also no evidence of ceiling or floor effects based on the distribution of scores. Regarding its clinical utility, the CRS-R reliably distinguished features of VS and MCS in a group of 80 patients with DOC, and identified 10 cases that were misdiagnosed as VS. Based on these findings, the CRS-R appears to meet minimal standards for measurement and evaluation tools designed for use in interdisciplinary medical rehabilitation.

### Individualized Behavioral Assessment

The rigorous attention to methodologic consistency afforded by standardized measures does not allow case-specific questions to be addressed. For example, standardized procedures may not be able to differentiate between random movement and low frequency movement to command because the investigational technique is fixed and the number of observations restricted. For example, finger movement that occurs on two of four trials immediately after the command to "move your fingers" raises the possibility of verbal comprehension. However, if finger movement fails to occur during the next 20 trials administered, the probability that the two

earlier responses represented evidence of verbal comprehension is diminished. Conversely, a patient may move his or her fingers following command on 10 consecutive trials but, if the same finger movement precedes the command, or persists well after the last command is administered, it is less likely that this response is an indication of verbal comprehension. To address this problem, DiPasquale and Whyte (46) developed an approach termed, "Individualized Quantitative Behavioral Assessment (IQBA)." IQBA applies principles of single subject research design to assess the cognitive and behavioral capacities of individuals with marked limitations in responsiveness. In this technique, clinical questions are individually tailored, stimuli and response criteria are operationally-defined and behavioral frequencies are analyzed statistically to determine whether the behavior of interest exceeds the rate predicted by chance. This approach has been successfully employed to investigate command-following, visual function, communication ability, emotional responses and drug efficacy (47).

Standardized and individualized procedures should be viewed as complementary as they serve different purposes. Standardized methods are designed to provide a broad overview of the integrity of sensory, motor and cognitive processes. When viewed *in toto*, these findings can help establish diagnosis, prognosis and lesion locus, and may inform the optimal approach to treatment. The inherent flexibility offered by the individualized approach provides an opportunity to control case-specific influences on behavior which contribute to diagnostic inaccuracy and erroneous judgements concerning consciousness.

### TREATMENT INTERVENTIONS AND EFFECTIVENESS

The primary goal in treating individuals with disorders of consciousness is to restore basic functional competence. The degree to which this goal can be achieved is dependent upon multiple factors including arousal level, sensorimotor functions, communication ability, initiation and drive mechanisms and executive control processes. Treatment strategies, therefore, are usually designed to improve or augment one or more of these areas. Unfortunately, no treatment has definitively been shown to alter the natural course of recovery from coma, VS or MCS. This may be due, in part, to the lack of prospective, randomized controlled clinical trials (RCTs). RCTs represent the gold standard for testing treatment effectiveness, but are particularly difficult to organize because they require large sample sizes, tight control over exposure to related treatments and an extended period of follow up. Not surprisingly, most of the published research on treatment efficacy consists of uncontrolled case studies and case series.

### Types of Treatment

Interventions available for individuals with disorders of consciousness can be grouped into three broad categories. Treatments that rely on *sensory stimulation (SS)* provide systematic exposure to a variety of environmental stimuli. The intent of SS is to improve arousal level and increase the frequency of purposeful behavior. Included within this category are environmental exposure strategies and structured sensory stimulation programs. *Physical management* strategies employ traditional rehabilitation techniques to promote physical health and prevent secondary complications. Interventions such as range of motion exercises, positioning schedules, bowel and bladder training, spasticity management and prevention of heterotopic ossification fall within this category. *Neuro-modulation* protocols are designed to promote recovery by directly altering the neurophysiologic substrate presumed to be responsible for mediating consciousness. Pharmacologic interventions and deep brain stimulation represent examples of neuromodulatory approaches. Table 25-3 provides an overview of the treatments described above.

### Treatment Efficacy

Treatment decisions should be guided by the strength of empirical evidence available for a particular intervention. A direct consequence of the lack of prospective RCTs on treatments for disorders of consciousness is that most existing efficacy studies have significant methodologic limitations that limit their interpretability and clinical application.

Research designs are often flawed and difficult to compare across studies. Diagnostic criteria are non-uniform, subject characteristics are inadequately reported, outcome measures are psychometrically weak or too insensitive to detect subtle but prognostically important changes over time and there is significant variation in the frequency and duration of the treatments employed. Nevertheless, the literature does provide some empirical information concerning the interventions used with this population.

*Sensory Stimulation* In a recently completed evidence-based review, Giacino (48) found that the majority of published studies of SS represent class III and IV evidence (49) which is primarily comprised of case studies and retrospective data analyses (50–53). No class I prospective randomized controlled trials (RCT) were identified. A class II RCT, completed by Johnson, Roethig-Johnston and Richards, (54) provided multimodal SS to 14 patients in coma or VS within 24 hours of injury. Biochemical and physiologic markers were monitored before and after SS. On average, the treatment group received SS for 8 days and the placebo group was treated for 4 days. The authors reported that there was a significant stimulation effect



**TABLE 25-3**  
**Overview of Treatment Interventions Utilized in Disorders of Consciousness**

TYPE OF INTERVENTION	RATIONALE	METHOD	INTENDED OUTCOME	EFFICACY STUDIES
<b>Sensory Stimulation</b>				
Environmental Exposure	Sensory enrichment prevents failure to thrive and loss of preserved functions	Exposure to naturally-occurring environmental stimuli/events (e.g. TV, music, group activities)	Activation of basic perceptual processes (e.g. visual scanning, sound localization)	No published studies
Structured Sensory Stimulation	Information processing efficiency is dependent upon proper calibration of stimulus intensity and response threshold	Administration of multi-modal sensory stimuli (e.g. auditory, visual, tactile, olfactory) titrated to existing sensory thresholds	Improve breadth and reliability of behavioral response repertoire	Hall, et al. (50) Wilson, et al. (51) Pierce, et al. (52) Wood, et al. (53) Johnson, et al. (54)
<b>Physical Management</b>				
	Health maintenance and physical re-conditioning maximize the likelihood and rate of recovery of spared neurologic functions	Implementation of range of motion exercises, positioning protocols, bowel/bladder schedules, skin care regimens, etc.	Prevention of aspiration, contractures, decubiti, malnourishment, heterotopic ossification, infection	Mackay, et al. (55) Timmons, et al. (57) Tanheco & Kaplan (58) Weber (59)
<b>Neuromodulation</b>				
Pharmacologic	Specific chemical agents may potentiate damaged neurotransmitter systems responsible for mediating attention and intention	Administration of cholinergic, dopaminergic, noradrenergic and serotonergic agonist medications	Improve arousal (i.e. wakefulness), alertness (i.e. vigilance) and intention (i.e. behavioral initiation)	Reinhard, et al. (61) Powell, et al. (62) Passler & Riggs (63) Meythaler, et al (64) Zafonte, et al. (65)
Deep Brain Stimulation	Electrophysiologic stimulation of the brain stem reticular system produces physiologic and behavioral changes associated with arousal	Chronic electrical stimulation of mesodiencephalic structures	Amelioration of arousal and/or cognitive deficits (e.g. neglect, memory disturbance) associated with disruption of thalamocortical circuits	Kanno, et al. (71) Tsubokawa, et al. (72) Schiff, et al. (73)

noted between groups at 6 days post-injury on only one of six biochemical markers. No difference was noted in biochemical or physiologic measures between survivors and deceased subjects. Of the remaining class III and IV studies (50–53), none were masked, approximately 50% provided inadequate subject and treatment descriptions and most lacked information necessary to determine the equivalence of the comparison group. In view of the dearth of methodologically sound studies involving SS, definitive conclusions regarding the effectiveness of this type of intervention cannot be drawn. Consequently, it is incumbent upon clinicians to clearly elucidate to family members, the high degree of clinical uncertainty associated with this form of treatment. To date, there have not been any published reports of harm associated with the use of SS.

*Physical Management* Despite the universal acceptance and widespread use of physical management strategies employed to facilitate recovery of consciousness and function, no prospective RCTs have been conducted to date. Mackay, et al. (55) completed a retrospective study to assess the effectiveness of an organized inpatient rehabilitation protocol on length of stay and cognitive outcome. Retrospective chart reviews were completed on 38 individuals with severe TBI (initial GCS of 3 to 8) consecutively discharged from an inpatient rehabilitation facility. Seventeen individuals received an aggressive, formal program of multi-disciplinary rehabilitation during the acute hospitalization. Treatment methods were designed to promote physical recovery and prevent complications. The 21 remaining individuals did not receive any formal rehabilitative treatment. There were no statistically significant



differences between the two groups on injury severity, brain stem reflexes, associated injuries or level of function on admission. Outcome data indicated that duration of coma and length of rehabilitation were approximately 66% shorter, discharge ratings on the Levels of Cognitive Functioning scale (LCFS) (56) were significantly higher and the percentage of home discharges was greater in the group that received the structured rehabilitation program. The generalizability of these findings is limited as they are based on a retrospective chart review and the authors provided only a cursory description of the treatment intervention.

Timmons, Gasquoine and Scibak (57) evaluated the degree of functional improvement noted in 47 patients who received interventions designed to promote health maintenance. All patients were admitted to rehabilitation at LCFS levels II to III within six months of injury. Since none of the patients reportedly showed functional communication, all were presumably in VS or MCS. Treatment consisted of interventions aimed at improving "physiologic integrity" and preventing complications. Procedures were administered by nursing staff and included hygiene procedures, positioning protocols, range of movement, pulmonary care and multisensory stimulation. By 12 months post-injury, 83% of the level III patients demonstrated functional improvement as compared to 31% of level II patients. Overall, 44% of the sample had regained functional communication, mobility or were able to use an upper extremity to perform activities of daily living. The authors suggested that amount of treatment influenced outcome since patients who did not improve received fewer hours of treatment than those who did (15 vs. 25 hours per week). This relationship did not appear to be related to length of time post-injury, however, the authors did not consider spontaneous recovery as a possible cause of the improvements noted.

Two additional case study reports describe functional improvement following introduction of physical management strategies. Tanheco and Kaplan (58) reported significant improvements in communication and self-care abilities in a 31 year-old woman with a six year history of eyes-closed coma resulting from a motor vehicle accident. The patient was admitted from a nursing home for inpatient rehabilitation after family members reportedly observed eye-opening, accurate head nods and occasional verbalizations. On admission, the patient was severely contracted with multiple decubiti, speech intelligibility was 10% to 25% and communication was compromised by vocal cord paralysis and limb contractures. Range of motion, stretching, serial casting and surgical releases were performed to facilitate motor function while breath control and single syllable vocabulary exercises were implemented to increase communication ability. An exercise regimen was begun to increase strength and

endurance. After approximately six months of treatment, the patient was discharged home. By fourteen months, she was able to self-feed and groom with set up and could dress and transfer with moderate assistance. She was able to communicate bowel and bladder needs and rarely experienced incontinence. The decubiti healed and active range of movement improved enough to allow her to use her right upper extremity for pointing. This case is of interest given the late re-emergence of consciousness and degree of functional recovery that occurred after physically-based rehabilitation strategies were initiated.

Weber (59) monitored EEG responses in 3 patients (2 TBI, 1 anoxic) with GCS scores of eight or below during the first week post-injury in a neurologic intensive care unit. The treatment condition involved two 30 minute sessions of sensorimotor facilitation consisting of passive ranging, quick stretch exercises and joint traction. This was followed by proprioceptive and thermal stimulation accompanied by verbal requests for movement. Each patient served as their own control and received two 30-minute non-treatment sessions in an A-B-A-B design. EEG recordings were obtained before and after exposure to the treatment or non-treatment conditions. Data analyses revealed differential EEG responses by treatment condition. There were significant voltage fluctuations in the bandwidth of the damaged hemisphere that were associated with the patient's "awake" state. Significant voltage changes were not noted in the damaged hemisphere during the non-treatment condition. EEG tracings also suggested normalization of sleep following treatment exposure in all three patients. Unfortunately, follow up data was not collected so it is not known whether the reactive EEG changes presaged a favorable outcome.

*Neuromodulation* Neuromodulatory approaches to treatment of disorders of consciousness seek to alter the neurophysiologic disturbances that accompany severe brain injury. Pharmacologic intervention is the most widely used form of neuromodulation. Drug therapy has been utilized to improve arousal, promote behavioral initiation and persistence, stimulate speech and reduce agitation. The "workhorse" agents used in rehabilitation of individuals with disturbances in consciousness generally fall into three medication classes- psychostimulants, dopamine agonists and tricyclic anti-depressants. There is some evidence that stimulants and dopamine agonists are effective for improving arousal (i.e., wakefulness) and basic attentional functions (60). Significant improvements in behavioral initiation and response persistence have been noted following administration of amitriptyline (61), bromocriptine (62, 63) and amantadine (64, 65). Recovery of spontaneous speech (66, 67) and increases in verbal fluency (62) have also been tied to the use of bromocriptine in individuals diagnosed with MCS.

There are few controlled medication trials in patients with disorders of consciousness. Meythaler and colleagues (64) recently conducted one of the few prospective, randomized, controlled trials completed to date. These investigators administered amantadine hydrochloride (100 mg, bid) or placebo to 35 patients who were one to six weeks post-injury and had Disability Rating Scale scores between 15 and 22. A crossover design was used in which half the group received amantadine first, followed by placebo, while the other half received placebo first, followed by amantadine. Results indicated that cognitive and functional improvement was more rapid during the on-drug phase, regardless of whether subjects received AH or placebo first. At three and six month follow-up, there was no significant difference in DRS scores between treatment groups. Two important methodologic problems challenge the authors' conclusions, however. The group that received amantadine first was less severely disabled prior to treatment than the placebo group and may have achieved more favorable outcomes independent of treatment. Second, because a crossover design was used early in the course of recovery, the group that received amantadine first had improved substantially at the point of crossover, limiting their opportunity to improve to the same extent as the comparison group during the second phase of treatment. By the time the group treated with amantadine first reached crossover, the range of possible improvement on the DRS had narrowed from 15 points (during the active drug phase) to 5 points (during the placebo phase).

In a multicenter observational study of 124 patients with TBI, of all stimulants and dopaminergic agents administered, only amantadine was associated with better outcome (DRS scores) at 4 months post-injury (77). A subanalysis of those who received amantadine indicated that significant improvement in DRS scores occurred just after amantadine was initiated, suggesting that the medication influenced the improvement in functioning.

Passler and Riggs (63) investigated the effectiveness of another dopaminergic agent, bromocriptine (2.5 mg, bid), in improving functional outcome in a series of five patients in VS. In this study, bromocriptine was used in association with multidisciplinary rehabilitation interventions. The authors reported that physical and cognitive recovery at 12 months post-injury was greater in the bromocriptine-treated patients, relative to a group of historical controls. The strength of this study is limited by the small sample size, questionable comparability of the historical control group and failure to adequately address the influence of spontaneous recovery on outcome. It should be noted that a number of studies have reported adverse behavioral and cognitive side effects associated with the use of dopaminergic agents, including agitation, perseveration (68) and exacerbation of neglect (69).

Deep brain stimulation (DBS) is a neurosurgical procedure in which electrical pulses are delivered through

electrodes implanted in brain stem or thalamic structures. This technique is derived from experimental findings in animals showing behavioral and EEG arousal responses in response to stimulation of the reticular system (70). One of the earliest clinical reports of DBS was described by Kanno and colleagues (71) and involved patients diagnosed with vegetative state. Clinical improvements were reported in three of the four patients treated and all four demonstrated improvements in EEG within two weeks of treatment. Improvements were noted in eye-opening, emotional expressiveness, verbal command-following and communication ability during the course of the trial. Tsubokawa and others (72) administered DBS to eight patients (TBI = 4, vascular = 3, anoxia = 1) who were reportedly in a vegetative state for more than six months. Stimulation was applied to sites in the mesencephalic reticular formation and non-specific thalamic nuclei. Behavioral changes associated with increased arousal, including opening of the eyes and mouth, vocalization and movement of the extremities, were observed in response to the stimulation. The behavioral changes coincided with desynchronization of the EEG and marked increases in regional cerebral blood flow and cerebral metabolic rates of oxygen and glucose. The authors noted that two of the eight patients recovered consciousness after 12 months post-injury.

Both of the DBS studies described above are compromised by significant methodologic flaws limiting their clinical applicability. Crude assessment and outcome measures were employed in both studies making it difficult to determine the accuracy of the patients' diagnoses as well as the nature and extent of the changes reported. Because neither study utilized a no-treatment control group, spontaneous recovery cannot be excluded to explain the improvement noted in some of the cases reported.

Schiff, Rezai and Plum (73) have recently proposed a re-designed protocol for DBS that focuses on activation of specific cortical fields via stimulation of carefully selected thalamic targets. In this approach, specific subdivisions of the intralaminar nuclei of the thalamus are stimulated to facilitate activation of damaged but still viable thalamocortical networks. This protocol is recommended for use with patients in MCS versus those in VS, given the that the former are more likely to have greater sparing of thalamocortical and corticocortical pathways relative to the latter, suggesting they may be better able to harness the stimulation effects.

There is a clear need for additional clinical trials of interventions designed to speed the pace of recovery from severe brain injury and improve functional outcome. Because relatively few rehabilitation centers offer services for patients with DOC, this can only be accomplished through multicenter collaborative studies. In the last year, a study of the effectiveness of amantadine hydrochloride, funded by the National Institute on Disability and Rehabilitation Research, was launched. This study involves

eight rehabilitation centers in the U.S. and one in Germany. The primary aims are to determine if amantadine improves functional outcome during inpatient rehabilitation beyond the effects of a placebo, and whether amantadine-induced improvements persist following drug washout.

## PROGNOSIS

Prognosis for patients with DOC has been analyzed with respect to three main outcome areas: recovery of consciousness, functional recovery and mortality. Outcome of VS and MCS are considered separately below. Most of the available information concerns patients in VS since MCS has only recently been operationally defined.

### Outcome Following VS

Over 10 years ago, the Multi-Society Task Force on PVS (11) analyzed all available reports on outcome of VS and summarized prognosis for recovery of consciousness and functional recovery, based on the Glasgow Outcome Scale (74). The report included data on 434 adults and 106 children with traumatic brain injury, and 169 adults and 45 children with nontraumatic brain injury – primarily anoxic brain injury and stroke. Prognosis for recovery was substantially better for victims of traumatic brain injury than those who sustained nontraumatic injury. Of adults with traumatic brain injury who were unconscious at least 1 month, 33% recovered consciousness by 3 months post-injury, 46% by 6 months and 52% by 1 year. Approximately 35% of patients with TBI who were still unconscious at 3 months, regained consciousness by one year; if still unconscious for 6 months, 16% regained consciousness by 1 year. Of those adults with nontraumatic brain injuries unconscious for 1 month, only 11% recovered consciousness by 3 months and 15% by six months. No person with nontraumatic injury regained consciousness after 6 months post-injury.

Prognosis in children was only slightly more favorable. For those children with TBI who were unconscious at 1 month, 51% regained consciousness by 6 months and up to 62% of children with TBI recovered consciousness at one year after injury. After nontraumatic injury, recovery of consciousness occurred mainly within the first 3 months (11%), but a very small percentage (2%) regained consciousness between 6 and 12 months. Table 25-4 shows a summary of these outcome data.

The Task Force concluded that prognosis for recovery of consciousness was very poor 12 months after traumatic injuries and 3 months after nontraumatic brain injury for both adults and children. They suggested the term *permanent vegetative state* for patients who were still unconscious beyond these intervals after injury. Although unlikely, the chance of recovering consciousness is not absolutely lost. There are several reports of

**TABLE 25-4**  
**Prognosis and Functional Outcome According to the Glasgow Outcome Scale at 1 Year After Prolonged Unconsciousness in Adults with Traumatic Brain Injury (TBI) or Nontraumatic Brain Injury (nonTBI)**

	TBI	NON-TBI
Unconscious at least 1 month:		
Death	33%	53%
VS	15%	32%
SD	28%	11%
MD	17%	3%
GR	7%	1%
Unconscious at least 3 months:		
Death	35%	46%
VS	30%	47%
SD	19%	6%
MD/GR	16%	1%
Unconscious at least 6 months:		
Death	32%	28%
VS	52%	72%
SD	12%	0%
MD/GR	4%	0%

(From: Multi-Society Task Force on PVS, 1994) (VS = vegetative state; SD = severe disability; MD = moderate disability; GR = good recovery).

later recovery of consciousness (11, 75) Childs and Mercer (75) pointed out that there is insufficient evidence in the Task Force study or any other studies to predict the incidence of late improvement. In fact, using the limited number of cases followed beyond 12 months in the Task Force report, they recalculated that the incidence of regaining consciousness after 12 months in that limited series of patients was 14%.

The Task Force report described functional outcome using the Glasgow Outcome Scale. By 12 months post-injury, more than one-half of the patients were *severely disabled*, nearly one-third were *moderately disabled* and a little more than an eighth achieved a *good recovery* level. Functional outcome was worse after nontraumatic injury; nearly three-quarters of those who regained consciousness were severely disabled at 12 months. Outcome for children was somewhat better at 12 months: one-half were severely disabled while most of the remainder achieved a good recovery. Older adults (>40 years old) tended towards a worse functional outcome, rarely improving beyond the level of severe disability.

According to the Task Force report, mortality is relatively high for patients in VS at least 1 month (82% at 3 years, and 95% at five years (11). Life expectancy improves the longer a patient in VS survives and younger patients have a greater chance for survival (76).

Although the Task Force analysis provides some general guidelines and probabilities for outcome after prolonged unconsciousness, outcome prediction for individuals with prolonged unconsciousness is difficult at best. A recent multicenter study of 124 patients with severely impaired consciousness (VS or MCS) of 1 month or more after TBI, examined a number of demographic, injury severity, functional and neuroimaging variables to predict outcome. Of all the variables tested, time from injury to initial rehabilitation evaluation, initial functional level in a rehabilitation facility and the rate of early functional recovery were highly predictive of both recovery of consciousness and functional outcome at 4 months post-injury (77).

Electrophysiologic studies may provide some information in determining prognosis after prolonged unconsciousness. Somatosensory evoked potential studies are useful in predicting permanent vegetative state after anoxic brain injury. Absence of the N20 potential in the presence of the earlier N14 potential is a very poor prognostic sign for recovery of consciousness (78). In general, the absence of cortical potentials indicates worse prognosis early in the course of recovery. The presence of the later cortical potentials does not necessarily carry a favorable prognosis. Cognitive event related potentials can provide additional prognostic information over SSEPs alone (79). A recent study by Fischer and others (80) demonstrated that if the cognitive evoked potential was present in patients with prolonged coma, the patient did not remain in a vegetative state. In that study, the best predictors for regaining wakefulness, though not necessarily consciousness, after coma of various etiologies were the presence of a pupillary reflex, followed by the presence of late auditory evoked potentials (N100) and middle-latency evoked potentials.

Structural neuroimaging (CT and MRI) is not very helpful in prognosticating outcome of impaired unconsciousness but there are some correlates with worse outcome. Kamplf and colleagues (81) found that location of brain lesions after trauma was a better predictor of recovery from prolonged unconsciousness than Glasgow Coma Scale scores, age and papillary abnormalities. Patients who did not recover consciousness by 12 months had a significantly higher frequency of corpus callosum, corona radiata and dorsolateral brainstem lesions than those that did regain consciousness. These locations are not specific for unconsciousness but are correlates of more severe grades of diffuse axonal injury (82).

### Outcome Following MCS

Functional outcome appears to be substantially better for patients in MCS than those in VS when evaluated during a similar time post-injury. In a small series of patients with impaired consciousness followed for 4 months, Rappaport (41) reported improvement in 25% of a small group of patients with impaired consciousness noting that only

those in MCS (referred to as “near-coma”) improved; none in VS improved in the follow-up period.

Although few prognostic studies of MCS have been completed, there is strong consensus that outcome from MCS following traumatic brain injury is highly variable, ranging from good recovery to severe disability on the Glasgow Outcome Scale (GOS) (74). The timeframe for establishing when MCS can be considered permanent is unclear as few empirical studies have addressed this particular subgroup.

Studies comparing functional outcome between individuals diagnosed with VS and MCS suggest that individuals in MCS show more rapid improvement, a longer period of recovery and significantly less functional disability at twelve months (77, 83, 84). Figure 25-2 depicts the results of a study conducted by Giacino & Kalmer (83) that investigated functional outcome on the Disability Rating Scale (DRS) (85) across the first year post-injury in patients diagnosed with VS or MCS. The VS and MCS groups were stratified further according to etiology of injury (i.e., traumatic or non-traumatic). Although both diagnostic groups presented with similar levels of disability at one month post-injury, outcome was significantly more favorable by twelve months in the MCS group, particularly after TBI. The differences in outcome became progressively more apparent at 3, 6 and 12 months post-injury. The probability of a more favorable outcome (moderate or no disability) by one year was much greater for the MCS group (38%) than the VS group (2%) and only occurred in those patients with TBI.

Giacino and Kalmar’s findings have recently been replicated and extended by Lammi and colleagues (84) who followed 18 patients in traumatic MCS for two to five years after discharge from an inpatient brain injury

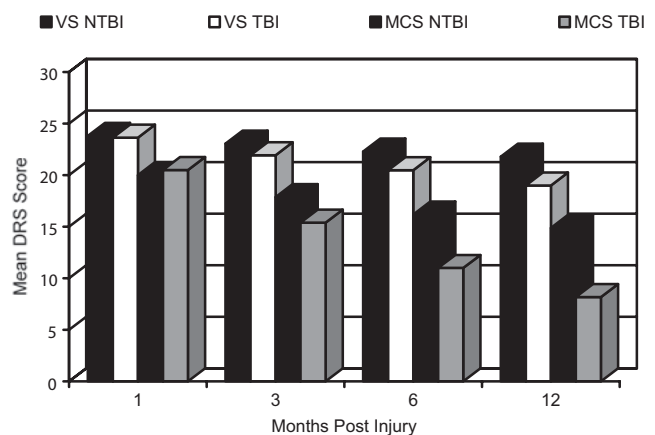


FIGURE 25-2

From “The vegetative and minimally conscious states: A comparison of clinical features and functional outcome,” by J.T. Giacino and K. Kalmar, 1997, *Journal of Head Trauma Rehabilitation*, 12(4), p. 42. Copyright 1997 by Aspen Publishers, Inc. Reprinted with permission



rehabilitation program located in Australia. The authors found that 15% of their sample had partial disability or less at follow-up while 20% fell in the extremely severe to vegetative category. In comparison, Giacino and Kalmar reported that 23% of their sample had no more than partial disability at 12 months with 17% classified as extremely severe to vegetative. In both samples, the most common outcome was moderate disability which occurred in approximately 50% of patients. Of particular importance, Lammi et al. also noted that duration of MCS was not correlated with DRS outcome and that 50% of their sample had regained independence in activities of daily living at follow-up. Both of these studies suggest a clear separation between MCS and VS in course of recovery and eventual functional outcome. Mortality following MCS appears to be similar to that of VS indicating that the presence of consciousness is not the critical factor predicting survival (86). Additional data concerning mortality after severe TBI is provided in the chapter by Shavelle, et al. in this volume.

### RECOMMENDATIONS FOR A RATIONAL APPROACH TO CLINICAL MANAGEMENT

In the absence of empirically-established standards of care for clinical management of individuals with disorders of consciousness, clinicians should adhere to a core set of basic tenets to guide evaluation and treatment of patients with DOC. In that spirit, the following recommendations are proposed, not as a prescriptive mandate, but rather, as a self-study reference for brain injury rehabilitation programs that offer services to this population.

#### Assessment Strategies

Carefully-defined *inclusion criteria* should be developed for patients with DOC seeking admission to rehabilitation programs. This population has unique needs that may not be easily accommodated by traditional rehabilitative interventions. Specialized training is essential for staff members responsible for providing assessment and treatment services as few academic programs directly address the care of patients with DOC. Diagnosis, cause of injury, length of time post-onset, degree of medical stability, age, level of disability and adequacy of support system are factors that should be considered in admission decisions as each one can influence outcome. Creation of a local database is useful for monitoring these variables and may help identify admission and discharge trends, gauge program effectiveness and facilitate longitudinal research.

A *comprehensive neuromedical work up* should be obtained on admission. This should include a complete review of the history, comprehensive physical examination, neurologic assessment, neuroimaging studies (if recent scans are unavailable), nutritional assessment and

review of current medications. Undetected or co-existing medical conditions such as post-traumatic epilepsy, hydrocephalus, late subdural hematoma, neuroendocrine dysfunction, nutritional deficiency, occult infection and drug toxicity must be excluded as potential causes of under-arousal and under-responsiveness (4).

A *well-defined assessment protocol* should be developed to monitor changes in neurologic, cognitive, physical and functional status. Standardized measures of neurobehavioral responsiveness (39–42, 44) and functional disability (85) should be utilized and supplemented with individualized assessment techniques (46), as needed. When conducting medication trials, outcome goals should be operationally-defined and objective measures employed to track progress. In most cases, patients should be serially reevaluated during the first three months post-injury to detect fluctuations in level of responsiveness. After the three month mark, assessment frequency should be determined by the patient's rate of change. Follow-up examinations should be completed at 12 months whenever possible as significant change is unlikely after this point.

There are no universally accepted *criteria for determining when rehabilitative treatment should be discontinued*. It is incumbent upon individual programs to determine local decision-making criteria to assure consistency across patients. There are four clinical factors that should be considered in the decision to discontinue treatment (48). The first two, cause of injury and length of time post-onset, represent important determinants of outcome, particularly when they are utilized in combination. As discussed earlier, the probability of recovering from VS after three months is significantly higher following traumatic versus non-traumatic brain injury (11, 83, 84). The patient's current level of neurobehavioral responsiveness is a third factor that should be taken into account as this reflects the extent of spared neural circuitry available to process sensoriperceptual input and mediate behavioral output. Response profiles dominated by reflexive brain stem activity offer little opportunity to promote higher-order cognitive processing given the loss of cortical connectivity. The fourth factor, rate of recovery, is perhaps the most important variable. Prior studies suggest that evidence of ongoing change is a favorable predictor of functional outcome, even in patient's who have not yet regained signs of consciousness (39, 77). The specific weight that should be assigned to each factor has not yet been elucidated. Additional research is needed before algorithms can be developed to guide treatment discontinuation decisions. This task should be viewed as an important objective in brain injury rehabilitation.

#### Treatment Strategies

Physical management interventions (e.g., range of motion, positioning, hygiene, etc.) should be considered a standard

component of the rehabilitation regimen of patients with disorders of consciousness. While it is unknown whether these interventions can facilitate the pace or degree of neurophysiologic recovery, there are strong rational indications for their use, and little evidence that they are ineffective or unsafe. Steps should be taken to ensure that comfort is maintained and pain alleviated, particularly when intrusive medical and rehabilitative procedures are performed. Other interventions such as sensory stimulation and medication trials should be considered treatment *options* and should be construed as supplementary to the basic rehabilitative strategies described above.

Special emphasis should be placed on utilizing behavioral and pharmacologic strategies to promote arousal and facilitate neurogenic drive. Preserved cognitive function may be masked by deficiencies in these areas. Alternative or augmentative communication systems should be implemented in individuals diagnosed with MCS because sensory and neuromuscular impairments often accompany disturbances in consciousness (5, 6). Assisted communication systems should not be incorporated into long-term care plans until there has been an adequate period of assessment in which response consistency and reliability have been demonstrated.

Finally, a formal protocol for providing family/surrogate education and training should be developed. An explicit mechanism for allowing ongoing communication between caretakers and the rehabilitation team across the span of treatment is a pre-requisite for effective treatment. At a minimum, family conferences should be held shortly after admission and prior to discharge. The initial conference should include discussion of the preliminary assessment findings, particularly those that pertain to functional capacity and prognosis for further recovery. The treatment objectives recommended by the clinical team should be presented and integrated with the goals stipulated by the caretakers. Specific treatment methods should be outlined and accompanied by information regarding the efficacy of the proposed interventions and the anticipated outcome in each targeted area. A second meeting should be held prior to discharge to confirm or modify the initial diagnostic and prognostic impressions, clarify recommendations for clinical management and to establish a plan for follow-up assessment, as indicated.

### ETHICAL CONSIDERATIONS

Neurorehabilitation specialists often encounter difficult ethical issues related to the clinical management of patients with DOC. While most clinicians have not received formal training in bioethics, it is important to have some awareness of the type of ethical questions that are likely to arise during the course of treatment. Comprehensive review of these issues is beyond the scope of this chapter but it is

useful to summarize some of the questions clinicians can expect to be confronted with during acute and post-acute care of these patients. For additional discussion of ethical considerations, interested readers are referred to the chapter by Kothari, et al. in this text and the recent special issue of *Neurorehabilitation* on scientific advances and ethical dilemmas concerning life-sustaining treatments in VS (87).

- Is it appropriate to allocate resources to the treatment of patients with chronic disorders of consciousness at the same level as patient's who are fully conscious?
- At what point should rehabilitative treatment be considered futile?
- What services should be provided after VS and MCS are deemed permanent?
- Is it appropriate to withdraw artificial nutrition and hydration in non-terminal patients in permanent VS and MCS?
- Should artificial hydration and nutrition be discontinued in patients in VS and MCS before criteria for permanence are met?
- Should patients with disorders of consciousness be permitted to participate in clinical trials?

### CONCLUSIONS AND FUTURE DIRECTIONS

Disorders of consciousness are arguably the most enigmatic conditions encountered in medical rehabilitation. Although progress has been made over the last decade in developing more reliable assessment methods, the psychometric integrity and clinical utility of these measures remain highly variable. Similarly, remarkably little is known about the neurophysiologic substrate underlying these disorders. These problems have been sustained, in part, by clinical nihilism – the belief that little effort should be invested in these patients because they cannot be helped. Recent initiatives to establish standards of care for evaluation and clinical management have begun to take hold and are expected to progress more rapidly in view of new insights gained from novel neurodiagnostic technologies.

At present, there are no treatment interventions that have been demonstrated to be effective in facilitating recovery of consciousness. Additional research is needed to 1) clarify the natural history of recovery from VS and MCS, 2) identify predictors of recovery of consciousness and cognition, 3) elucidate the pathophysiology underlying specific disorders and 4) develop treatments capable of altering outcome in patients with DOC. To accomplish these goals, it will be necessary to establish collaborative partnerships across rehabilitation centers and across disciplines. In the current healthcare climate, few rehabilitation centers can recruit patient samples large enough to carry out adequately powered clinical trials. Moreover, most centers do not have

ready access to neuroscientists, biophysicists, neurosurgeons, neurologists and bioethicists, all of whom contribute uniquely to the study of patients with DOC.

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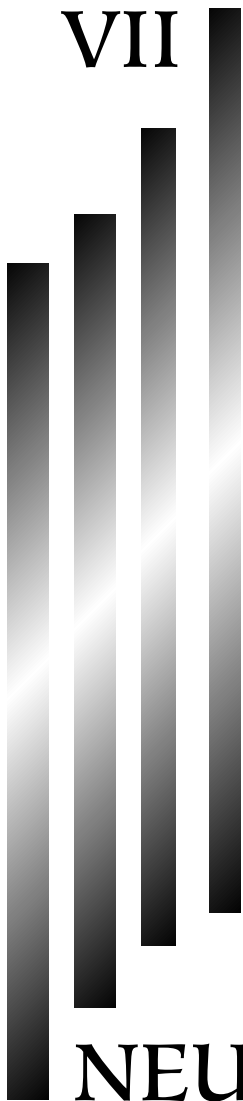


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VII



NEUROLOGIC PROBLEMS

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# 26

## Post-Traumatic Seizures and Epilepsy

**Stuart A. Yablon**  
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### INTRODUCTION

Traumatic brain injuries (TBI) remain a leading cause of neurologic disability and death in the population of the United States and westernized nations. While the incidence of hospitalization for mild TBI in the United States has declined (1), the number of patients hospitalized for TBI remains significant, approximately 100/100,000 per year (1). Among the survivors of TBI, a sizable number remain with important medical and neurological sequelae, including seizures.

The relationship between TBI and subsequent development of post-traumatic seizure (PTS) disorders, including incidence, risk factors for initial occurrence and recurrence, and management, comprise the central themes of this review. Most cited studies address PTS among adults. Issues pertinent to diagnostic and therapeutic management of PTS in the patient with severe traumatic brain injury (TBI) are emphasized.

### CLASSIFICATION OF POST-TRAUMATIC SEIZURES AND EPILEPSY

It is useful to review terms employed in the discussion of post-traumatic seizure disorders. These are defined in the Practice Parameter on the Antiepileptic Drug Treatment of Post-traumatic Seizures by the Brain Injury Special

Interest Group of the American Academy of Physical Medicine and Rehabilitation (2) (Table 1), and the Guidelines for Epidemiologic Studies on Epilepsy, by the Commission on Epilepsy and Prognosis of the International League Against Epilepsy (3). An *epileptic seizure* is a clinical manifestation presumed to result from an abnormal and excessive discharge of a set of neurons in the brain. The clinical manifestation consists of sudden and transitory abnormal phenomena, which may include alterations of consciousness, motor, sensory, autonomic, or psychic events, perceived by the patient or an observer (3). *Epilepsy* is a condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause (3).

*Post-traumatic epilepsy* (PTE) is a disorder characterized by recurrent late seizure episodes, not attributable to another obvious cause, in patients with TBI (2). Although PTE has commonly designated single or multiple seizures, including early seizures, the term should be reserved for recurrent, late PTS. Since most studies regarding seizures among patients with TBI do not address recurrence, the term post-traumatic seizures (rather than epilepsy) is preferred, since it encompasses both single and recurrent episodes. Thus, a *post-traumatic seizure* (PTS) refers to a single or recurrent seizure episode occurring after TBI (2). Post-traumatic seizures have been further classified into early (< 1 week after TBI) and late (>1 week after TBI) categories, primarily due to prevailing

opinion that they represent similar manifestations of different pathophysiologic processes (4). Classification of early seizures as those occurring within the first seven days after TBI has sparked some controversy (5), particularly with regard to long-term AED treatment decisions. There is little data to suggest that seizures that occur at day 8 or 14 have recurrence characteristics that justify classification as late seizures, and underlying mechanisms of seizure appearance are more likely to reflect acute pathophysiologic processes rather than those of chronic epilepsy.

The exclusion of "other obvious causes" is especially relevant to this patient population. Seizures occurring among patients with TBI may be the result of precipitants unrelated to mechanisms currently linked with post-traumatic epileptogenesis. Seizure precipitants have been defined as any endogenous or exogenous factor that promotes the occurrence of epileptic seizures (6). Examples of seizure precipitants among patients with TBI include hydrocephalus (7), sepsis (8), hypoxia (9), metabolic abnormalities (10) and mass-occupying lesions, including hemorrhage (11, 12). Among epileptic patients, more than 60% cite precipitants among recurrent seizures they experience. (6)

Drugs (13, 14), including alcohol (15, 16), prescribed psychotropic agents (14, 17–22), and recreational/illicit drugs (13, 23) warrant particular scrutiny as seizure precipitants among patients with TBI. In one study, for example, 19% of patients with severe TBI developed seizures attributed to tricyclic antidepressants (22). Antidepressants other than tricyclic agents are also implicated with seizure occurrence, including immediate (21) and sustained-release formulations of bupropion (17). While SSRIs are considered to have lower proconvulsant activity than other common antidepressants (24–26), several uncontrolled case studies of epileptic patients with depression have reported that SSRI administration increased seizure frequency (27, 28). Certain antipsychotic drugs, including newer atypical antipsychotic agents, particularly clozapine, may induce EEG abnormalities and seizures (18). Antibiotics, particularly imipenem (29) and quinolone agents (30), have been associated with seizures. Seizure risk is generally elevated among critically ill patients (31), however, and proper dose adjustment for renal clearance may mitigate much of the risk attributed to antibiotic administration (31, 32). Bromocriptine and amantadine, dopamine receptor agonists used to treat impaired arousal after TBI, have been implicated as seizure precipitants (33), although this association presently appears to be largely anecdotal. Recreational/illicit stimulants with well-known seizure-inducing properties include cocaine; however, few are probably aware that caffeine at high doses may also induce epileptic seizures (34). Amphetamine and related drugs rarely induce epileptic seizures at therapeutic doses (34). Moreover, methylphenidate and dextroamphetamine do

not appear to be associated with increased seizure risk among patients with TBI (33, 35).

Seizures and seizure disorders are classified according to their clinical and electroencephalographic characteristics, as developed by the Commission on Classification and Terminology of the International League Against Epilepsy (36, 37). Seizures have been divided into two categories, based primarily on pattern of onset. These include partial or focal seizures, and generalized seizures. Patients with nonpenetrating TBI frequently have sustained multiple foci of cerebral injury (38–40), and may manifest more than one type of seizure (4).

Generalized seizures denote those that are bilaterally symmetrical in origin without local onset (36). The most commonly recognized example is the grand mal, or tonic-clonic (GTC) seizure. Generalized-onset or secondarily generalized seizures (SGS) are reported in approximately half of the patients with PTS (41) and appear more frequently in patients with nonpenetrating TBI (42), and among children (43).

Partial or focal seizures originate in a localized area of one cerebral hemisphere. Partial seizures are further classified according to whether consciousness is maintained (simple partial [SPS]) or impaired (complex partial [CPS]) during the seizure. Characteristics of both vary, depending on the location of the seizure activity within the brain. Twelve percent of cases of CPS in the general population may be attributable to TBI (44). Partial-onset seizures are observed in slightly more than half of all patients with PTS, and appear more frequently in adults (4), and patients with early seizures (4, 42, 45), focal lesions on CT (46), penetrating TBI (PTBI) (42, 47), and nonpenetrating TBI of greater severity (46). Studies that incorporate videoelectroencephalography (VEEG) are more likely to detect subtle clinical signs that may indicate partial-onset PTS (48, 49).

The Working Group on Status Epilepticus (50) defines *status epilepticus* (SE) as more than 30 minutes of (1) continuous seizure activity or (2) two or more sequential seizures without full recovery of consciousness between seizures (50). More recent publications define SE as seizures that persist for shorter durations, (52, 51), based upon estimates of the duration necessary to cause injury to central nervous system neurons (51). This definition differs from those of other terms describing multiple seizure episodes, including serial seizures and acute repetitive seizures. *Serial seizures* are two or more seizures occurring over a relatively brief period (i.e., minutes to many hours), but with the patient regaining consciousness between the seizures (51). *Acute repetitive seizures* are clusters of seizures that appear to increase in frequency or severity over a short time. Acute repetitive seizures may become SE, but the frequency of this occurrence is unclear (53). Clinical manifestations of SE vary, and may include clinically obvious tonic-clonic movements, or small amplitude

twitching movements of the eyes, face, or extremities (51). Some patients have no observable repetitive motor activity, and the detection of SE requires EEG. Further discussion regarding status epilepticus after TBI follows later in this review.

Nonepileptic seizures, (NES) often called pseudo-seizures or psychogenic seizures, are terms used for episodic behavioral events which superficially resemble epileptic attacks but which are not associated with paroxysmal activity within the brain (54). NES may be psychogenic, or may include non-epileptic events such as syncopal episodes and cardiac events. NES are not uncommon in neurologic settings (55), and may coexist with epileptic seizures in patients with epilepsy (55, 56). The differentiation between nonepileptic and epileptic seizures cannot be made on the basis of clinical characteristics alone. Electroencephalographic monitoring (particularly with video) (56) is often helpful in establishing a diagnosis. Postictal prolactin (PRL) measurement (57) may provide additional diagnostic information if significant elevations are observed, suggesting that an epileptic seizure has occurred within one hour (58). The utility of this test to discriminate between epileptic seizures and NES has been questioned, however, as a subset of patients with video-electroencephalography (VEEG)-documented psychogenic NES have also been reported to experience an increase in PRL, particularly if the sample is obtained within 10–20 minutes of a suspected NES (58).

While recognized to occur among patients with TBI, relatively few studies address post-traumatic NES. Hudak et al reported that one-third of patients with moderate-to-severe TBI undergoing VEEG for diagnosis of epilepsy were found to have psychogenic NES (48). When non-diagnostic VEEG studies were excluded, patients with NES comprised 40% of the TBI sample (48). Barry et al. described the characteristics of 16 patients thought to have PTS, who actually had NES, as confirmed on VEEG monitoring. Patients with NES were characterized by injuries of much milder severity, although the disability associated with the NES was pronounced. The patients usually had manifestations of other conversion disorders as well, and psychiatric histories that predate the TBI (59).

Epilepsy has been classified into different epileptic syndromes, with two general divisions employed (3, 37). One division separates epilepsies characterized by generalized seizures from syndromes characterized by seizures of focal onset, termed localization-related epilepsies. The other division separates epilepsies of known etiology (secondary or symptomatic) from those that are idiopathic (primary) and those that are cryptogenic (seizures or epilepsy in which no known risk factor has been identified). Symptomatic epilepsies and syndromes are considered the consequence of a known or suspected disorder of the central nervous system, such as TBI (3, 37). Recurrent late post-traumatic seizures, or post-traumatic epilepsy,

are a common and important type of remote symptomatic epilepsy (3), accounting for 20% of all symptomatic epilepsy in the general population (60). Symptomatic (or secondary) epilepsies comprise syndromes of great individual variability, based mainly on seizure type and anatomic localization.

### MANIFESTATIONS OF POST-TRAUMATIC SEIZURES AND EPILEPSY

Seizures may present with a variety of manifestations, including cognitive, behavioral and affective changes that may not be attributed to an underlying epileptic disorder (61, 62). Patients with severe TBI may exhibit cognitive, behavioral, and affective sequelae that potentially confound attribution of episodic behavioral changes to an underlying epileptic disorder (48). The varied semiology of seizures that originate in the frontal or temporal lobes, and their associated ictal or postictal alteration of consciousness, justify their consideration in the differential diagnosis of any TBI patient with episodic (especially stereotypic) changes in mental status. Given the propensity of TBI contusion localization to the frontal and temporal lobes (40, 63), it is not surprising that these regions are the most frequent sites of origin for VEEG-verified partial-onset PTE (48). Presumed or pathologically-confirmed post-traumatic seizure foci, however, have been described in all major lobes of the brain (38, 48, 63–65).

Patients with frontal lobe epilepsy may exhibit complex, semipurposful, complex motor automatisms such as kicking, screaming, and thrashing episodes (62). Frontal lobe interictal and postictal manifestations also include cognitive or affective symptoms, such as confusion, anger, hostility, and hallucinations (66, 67). Complex partial seizures of temporal lobe origin may also present with emotional symptoms such as fear or panic, followed by periods of postictal confusion and amnesia (37). Seizure-related aggression, however, is rare (68, 69). It is usually associated with postictal confusion, particularly while the patient is being restrained (69, 70). Conversely, reports of aggression are more frequent among epileptic patients, particularly with younger age, male gender, psychopathology, and prior brain injury (71), but aggression episodes are typically unrelated to seizure type, frequency, or age of onset (72). Conventional interictal scalp EEG are of limited diagnostic assistance in such cases. Electrographic manifestations of seizure activity in the orbitofrontal and mesial temporal regions of the brain may be difficult to recognize, and can be misleading (62) by showing no abnormality (37) at all. Table 26-1 shows the characteristics of localization-related epilepsies based upon the involved lobe of the brain (37, 67, 73–79).

**TABLE 26-1**  
**Characteristics of Localization-Related (partial-onset) Epilepsies**

SITE OF ORIGIN	MANIFESTATIONS
<b>Frontal</b>	<p><b>Seizure types:</b> SPS, CPS, SGS, combinations; SE is frequent complication. Seizures often occur several times a day, and frequently during sleep.</p> <p><b>Features:</b> Features strongly suggestive of frontal lobe epilepsies include: 1) Generally short seizures; 2) CPS often with minimal/no postictal confusion; 3) rapid secondary generalization; 4) prominent tonic/postural motor manifestations; 5) complex gestural automatisms at onset (frequent); 6) falling with bilateral discharge (frequent).</p>
<b>Cingulate</b>	<p><b>Features:</b> CPS with complex gestural automatisms at onset; autonomic signs (common); changes in mood and affect (common); psychic/emotional auras, including fear and anger (frequent).</p>
<b>Orbitofrontal</b>	<p><b>Features:</b> CPS with initial sudden, complex, bizarre motor and gestural automatisms that may be bilateral and mixed with staring, olfactory hallucinations/illusions and autonomic signs; psychoemotional auras are rare.</p>
<b>Dorsolateral</b>	<p><b>Features:</b> Tonic (common) or clonic (less common) with versive eye and head movements and speech arrest. <i>Dorsolateral premotor cortex</i>-onset usually without aura, with tonic head/neck/eye movement or "pseudoabsence" (very brief lapse of consciousness &lt;10 sec duration); <i>Pre-frontal/Frontopolar</i>-psychic auras, visual illusions, or initial loss of consciousness followed by head and eye movements.</p>
<b>Motor Cortex</b>	<p><b>Features:</b> SPS (most common) with manifestations reflecting the side and topography of the area involved: <i>Lower prerolandic area</i>-speech arrest, vocalization or dysphasia, contralateral tonic-clonic movements of the face, or swallowing. Generalization is frequent. <i>Rolandic area</i>-SPS without "march" (jacksonian seizures), particularly beginning in contralateral upper extremity. <i>Paracentral lobule</i>-tonic movements of the ipsilateral foot and contralateral leg, postictal paralysis (frequent).</p>
<b>Supplementary Motor Cortex</b>	<p><b>Features:</b> Postural, focal tonic seizures, with vocalization, speech arrest, and fencing postures; usually no aura; may have autonomic symptoms.</p>
<b>Temporal</b>	<p><b>Seizure types:</b> SPS, SGS, CPS, combinations.</p> <p><b>Features:</b> Features strongly suggestive of temporal lobe epilepsies include: 1) SPS typically characterized by autonomic and/or psychic symptoms and certain sensory phenomena (e.g. olfactory and auditory), epigastric, often rising, sensation (most common); 2) CPS with onset of motor arrest or stare followed by oro-alimentary automatism (often), other automatisms frequently follow. Aura is common. Seizure duration typically &gt;1 min, with postictal confusion/amnesia, and gradual recovery (common); 3) Interictal scalp EEG with no abnormality, slight or marked asymmetry of background activity, or temporal spikes, sharp waves, not always confined to the temporal region. Ictal scalp EEG onset may not precisely correlate with clinical onset.</p>
<b>Mesiobasal / Limbic</b>	<p><b>Features:</b> CPS with visceromotor and behavioral symptoms, including rising epigastric discomfort, nausea, marked autonomic signs, and other symptoms, including belching, pallor, fullness/flushing of the face, respiratory changes, pupillary dilatation, fear, panic, and olfactory-gustatory hallucinations. Auditory symptoms do not occur. Interictal scalp EEG may be normal.</p>
<b>Lateral</b>	<p><b>Features:</b> SPS with auditory hallucinations or illusions or dreamy states, visual misperceptions; or language disorders (dominant hemisphere). May progress to CPS with propagation to mesial temporal or extratemporal structures. The scalp EEG may show unilateral, bilateral midtemporal or posterior temporal spikes.</p>
<b>Occipital</b>	<p><b>Seizure types:</b> SPS, SGS, CPS. CPS may occur with spread beyond the occipital lobe.</p> <p><b>Features:</b> Usually visual manifestations, appearing in the visual field contralateral to the discharge (unless generalization occurs). Nonvisual symptoms have been reported, but most often reflect spread to other lobes.</p> <p><i>Positive phenomena:</i> Visual hallucinations (most common), including sparks, flashes. Visual illusions have been reported, but probably reflect non-dominant parietal lobe involvement.</p>

**TABLE 26-1**  
(continued)

SITE OF ORIGIN	MANIFESTATIONS
<b>Parietal</b>	<p><i>Negative phenomena:</i> Ictal amaurosis, fleeting scotoma, hemianopsia. (well-recognized but less common).</p> <p><b>Seizure types:</b> SPS (most common), SGS (especially with paracentral lobule), CPS.</p> <p><b>Features:</b> Predominantly sensory with many characteristics, also some rotatory or postural motor phenomena may occur.</p> <p><i>Positive phenomena:</i> Most common: (tingling, electric shock-like sensations, desire/sensation of movement in body part) usually involving hand, arm and/or face contralateral to seizure focus. Less common: intraabdominal sensation of sinking/nausea, particularly with inferior and lateral parietal lobe involvement. Rare: pain, visual phenomena occurring as formed hallucinations.</p> <p><i>Negative phenomena:</i> numbness (common), disturbance in body image (a feeling that a body part is absent, asomatognosia [loss of awareness of a part or a half of the body, particularly with nondominant hemisphere involvement]), severe vertigo or spatial disorientation (inferior parietal lobe), receptive or conductive languages disturbances (dominant parietal lobe), lateralized genital sensation (paracentral parietal lobe).</p>
<b>Insula</b>	<p><b>Seizure type:</b> SPS</p> <p><b>Features:</b> Throat/laryngeal discomfort, paresthesias on contralateral (typical) side of body, dysarthria/aphonia, hypersalivation.</p>

### Ictal versus Postictal Focal Neurological Deficits

The presence of focal motor, sensory or language deficit of new-onset should alert the clinician to the possibility of a recent unwitnessed PTS. Todd's phenomenon/a are terms given to a heterogeneous group of focal signs of neurologic dysfunction that may follow a partial (9) or generalized tonic-clonic seizure (80). Todd's phenomena are recognized postictal manifestations of PTS (81). These do not reflect permanent structural damage, but rather represent transient *postictal* disruption of function that typically resolves within 24 to 48 hours (9). Todd's phenomena should be differentiated from ictal paralysis, a "negative" *ictal* epileptic manifestation, (82).

### Unclassified Phenomena (not considered to be post-traumatic seizures)

Transient behavioral changes, reminiscent of CPS (83–85), have been noted among TBI patients without concurrent seizures. In most reports, patients manifest interictal discharges on EEG, without the hypersynchronous EEG activity and stereotyped behaviors which characterize partial seizures and localization-related epilepsies (84, 85). When described among patients with TBI, these are usually reported among individuals with mild injury severity (84, 85). In these reports, many patients respond favorably to AEDs such as carbamazepine (CBZ) (85).

The resemblance of the behaviors to some CPS of temporal or frontal lobe origin, and favorable response to AEDs, tends to confuse clinical diagnosis. At present, the description of these behavioral abnormalities should not be considered diagnostic for epileptic seizures.

### INCIDENCE OF POST-TRAUMATIC SEIZURES

Traumatic brain injuries are an important cause of epilepsy, accounting for 20% of symptomatic epilepsy observed in the general population, and 5% of all epilepsy (60). TBI is the leading cause of epilepsy in young adults (86). Many studies addressing the relationship between TBI and epilepsy derive from observations of veterans sustaining PTBI in battle (47, 87–99). Studies in civilian settings (4, 39, 41, 43, 46, 100–129) generally appeared later and reflect a larger patient population with nonpenetrating TBI, as opposed to PTBI. The observed results vary, reflecting differences in inclusion and exclusion criteria, methods for evaluation and description of seizure phenomena, attention to confounding variables, duration of follow up, and patient population studied (130). Nevertheless, these studies provide useful information regarding the incidence, risk factors, and natural history of PTS/PTE.

In summary, the overall incidence of late seizures in hospitalized patients following nonpenetrating TBI is



approximately 4–7%, varying with the injury and patient characteristics (4, 102). Late seizures are observed less frequently among children (43, 102, 122). The incidence of PTS among patients with nonpenetrating TBI observed in the rehabilitation setting appears substantially higher than that reported in other civilian settings (103, 107, 108, 113, 118, 125, 127, 131), approximately 17%. This is probably a reflection of the increased severity of injury and concurrence of multiple risk factors encountered among inpatients in these settings (103, 113). In contrast, the incidence of seizures among adults after mild TBI is slightly greater than that observed in the general population (101, 102). PTS will be observed in approximately 35–65% of patients with PTBI (47, 88, 91, 92, 113). Discussion regarding the influence of specific risk factors upon the incidence of PTS follows later in this chapter.

The incidence of early seizures is approximately 5% (4, 132) among all nonpenetrating TBI patients, and is higher in young children (4, 42, 43, 102, 104), among whom the incidence is approximately 10% (43, 102). However, continuous EEG monitoring of patients with severe TBI in the intensive care unit suggests that the incidence of early convulsive and nonconvulsive EPTS may be considerably higher than initially believed, approximately 22% (49). Immediate seizures, which make up 50–80% of EPTS (4, 42, 93, 122, 133), are particularly frequent among children with severe TBI (43, 102). EPTS are occasionally observed among children with mild TBI (4, 43), but are comparatively much less frequent among adults with mild TBI. Early seizures among these adults warrant investigation for an underlying intracranial hemorrhage. In a study of >4000 adults with mild TBI, an intracranial hemorrhage was found in almost half of the patients with EPTS (123).

The incidence of early seizures is approximately 10% (43, 102) among young children (4, 42, 43, 102). Immediate seizures, which make up 50–80% of EPTS (4, 42, 93, 122, 133), are particularly frequent among children with severe TBI (43, 102). Late seizures are observed less frequently among children (43, 104, 122) than adults.

## NATURAL HISTORY OF POST-TRAUMATIC SEIZURES AND EPILEPSY

### Onset

Approximately one-half to two-thirds of patients who suffer PTS will experience seizure onset within the first 12 months, and 75–80% by the end of the second year following injury (41, 46, 47, 92, 96, 97, 109). After five years, adults with mild TBI do not appear to have a significantly increased risk relative to the general population (101). However, patients with moderate or severe TBI and PTBI remain at increased risk after this postinjury duration (42, 46, 47, 101).

### Recurrence

It is increasingly evident that seizure recurrence is a critical factor in determination of subsequent disability, and quality of life (135, 134). Greater seizure frequency significantly correlates with lower employment rates, which in one study ranged from 57% among patients seizure-free for 3 months, to 30% in patients with daily seizures. As seizure frequency increased, health care costs increased and measures of QOL declined (135).

Limited data exist regarding PTS recurrence. Earlier studies reported that about one-half of patients will experience a single PTS without recurrence (110, 122), and another quarter will suffer a total of 2–3 seizures (122). These reports addressed recurrence following early seizures. Recent studies addressing LPTS recurrence, however, suggests a more ominous prognosis (136, 137). Semah et al investigated the relationship between prognosis for seizure recurrence and the etiology of epilepsy. Among 50 patients with remote symptomatic epilepsy with history or radiographic evidence of TBI, only 30% of those with partial epilepsy experienced seizure free durations of >1y without recurrence (137). Haltiner and colleagues followed 63 adults with moderate or severe TBI, who developed LPTS during the course of participation in a randomized, placebo-controlled study of the effectiveness of phenytoin prophylaxis for prevention of LPTS (138). The cumulative incidence of recurrent late seizures was 86% by 2 years. However, 52% experienced at least 5 late seizures, and 37% had 10 or more late seizures within 2 years of the first late seizure (136).

Pohlmann-Eden (41) published results of a PTE study population derived from a tertiary referral epilepsy clinic. Fifty-seven patients with PTE were compared with 50 age and sex-matched control patients with severe TBI. Of all PTE patients, 35% became seizure-free (no seizures within the last 3 years), 3.5% without any treatment. Twenty-one percent experienced more than 1 seizure per week. The most important risk factors for poor seizure control were missile injuries, “combined seizure patterns,” high seizure frequency, AED non-compliance and alcohol abuse (41).

In summary, recent evidence suggests that while patients with EPTS will experience a late seizure in 20–30% of cases, seizure onset after the first week is associated with a much higher likelihood of seizure recurrence (97, 136). Seizure frequency within the first year after injury may be predictive of future recurrence, particularly with PTBI (47). Persistent PTS may be more common in partial seizures, and less common in generalized seizures (47, 137). IPTS are generally believed to carry no increased risk of recurrence (4, 139). On the other hand, between one-fifth to one-third of patients with LPTS will experience frequent recurrences, apparently refractory to conventional AED therapy (41, 131, 136). Some of these patients may be helped with surgical intervention (38, 64, 140). TBI neuroimaging characteristics may be of value

in predicting the appearance (113) and intractability (141) of PTE. Finally, few studies explicitly address rates of PTE remission, that is, disappearance of seizures (142). Early studies, derived mostly from PTBI populations, describe remission rates that range from 25–40%. Higher overall remission rates are reported in studies conducted after the development of effective AEDs (142).

### Complications and Consequences of PTS

Potentially significant complications accompany seizures in the patient with TBI. Indeed, occurrence or recurrence of seizures is an important cause of non-elective rehospitalization (143) and death (144) among patients with severe TBI. Among patients with newly-diagnosed (145) or chronic remote symptomatic epilepsy, persistent seizures are associated with increased mortality, particularly among individuals with status epilepticus or generalized convulsions (146). Several studies have examined the sequelae of PTS (147–150). An appreciation of these potential consequences is useful when evaluating risk/benefit relationships for decisions regarding AED therapy.

#### *Cognitive and Behavioral Function*

As introduced earlier, manifestations of PTS include cognitive and behavioral dysfunction. Evidence of cognitive impairment may occur or persist during the interictal state, however, when the epileptic patient is not actively manifesting seizures (151–153). Similarly, persistent behavioral abnormalities and a significantly higher incidence of psychiatric-related hospitalizations have been noted among patients with PTS when compared with non-epileptic controls with PTBI (154). Mazzini et al (125) found that disinhibited behavior, irritability, and aggressive behavior were significantly more frequent and severe among rehabilitation inpatients with PTE, when compared with TBI patients without seizures.

#### *Influence on Neurological Recovery*

Animal studies suggest the existence of a complex relationship between post-traumatic seizures and neurological recovery (155). Specifically, depending on the severity of the seizure induced and time of presentation, seizures may inhibit, improve, or not affect functional recovery. In studies conducted with rodents, if “mild” subclinical kindled seizures occur early after brain damage, no delay is noted in somatosensory recovery. This suggests that brief infrequent PTS occurring during the early post-traumatic period did not adversely affect functional recovery. However, if more severe and widespread seizures are kindled within a 6-day critical period after brain lesion, a permanent impairment of functional recovery results. When these same seizures occur after this

critical period, recovery of function proceeds unimpeded. It is important to note that contrasting results have been found using models of brain injury other than kindling models (155).

#### *Outcome*

Recurrent PTS may exert an adverse impact upon functional status among adults (156) and children (105) with TBI, independent of that attributable to the severity of injury. Among patients with PTBI in the Vietnam Head Injury Study, PTS were one of seven impairments which independently and cumulatively predicted employment status (156). PTS and increasing brain volume loss have been noted to exert independent and profound effects on cognitive performance among patients with restricted frontal lobe lesions due to PTBI (157).

However, studies among patients with nonpenetrating TBI less clearly discriminate the influence of seizures on functional prognosis (103, 104) and cognition (158) from those of injury. Haltiner (159) examined the relationship of LPTS to neuropsychological performance and aspects of psychosocial functioning. While patients with LPTS demonstrated greater impairment than those without seizures, after adjusting for injury severity, there were no significant differences in outcome at 1 year as a function of seizures. The authors concluded that poorer outcomes encountered among patients with PTS at 1 year postinjury reflect the severity of injury and not the effects of LPTS *per se*. Asikainen noted that patients with PTS had poorer outcome as measured by the Glasgow Outcome Scale (GOS), a gross global outcome measure, but no significant differences in employment outcome when compared with nonepileptic patients with TBI (104). Mazzini (125) also found that PTS correlated with significantly poorer outcome, as measured by the GOS, disability rating scale, functional independence measure, and subscales of the neurobehavioral rating scale at one year after severe TBI. In contrast, early seizures appear to have little influence on outcome (132, 160).

#### *Status Epilepticus*

Status epilepticus is the most clinically significant manifestation of PTS, and carries the greatest risk of adverse outcome. It may cause additional neurologic injury, potentially occurring within 10 minutes of seizure onset, according to some reports (161). One study employing continuous EEG monitoring suggests that early nonconvulsive SE may not be rare, occurring perhaps in as many as 6% of patients with severe TBI despite “therapeutic” levels of AED prophylaxis (49). Moreover, status epilepticus among patients early after TBI is associated with a very high mortality risk (49). Fortunately, *convulsive* SE remains an infrequent manifestation of PTS (122).

Additionally, SE is usually attributable to another cause, such as antiepileptic drug (AED) withdrawal, acute systemic or neurologic injury, such as anoxic encephalopathy or stroke (162), sepsis, metabolic derangements, or a combination of these conditions (8). Status epilepticus is more likely to be encountered as a PTS manifestation in children, (163). Deaths associated with SE are usually attributable to the disorder which precipitated it (164, 165).

### *Mortality*

Mortality among patients with PTS remains consistently elevated in most reports (147, 149, 150, 166). However, the contribution of PTS to this increased mortality is unclear. Walker noted that men with PTS have a death rate somewhat exceeding that of comparable normal men. However, information supplied by relatives suggested that causes of death were not specific for men with TBI, and seemed to reflect those found in elderly people (149). In another related series of studies, deaths among PTBI patients with PTS appeared due to the sequelae of injury and unrelated to seizures. These patients approached the actuarial mortality norm for their peers after only 3 years (133, 148).

Sudden unexpected death in epilepsy (SUDEP) accounts for 18% of all deaths among patients treated in major epilepsy centers (167). Walczak and colleagues noted that occurrence of tonic-clonic seizures, treatment with more than two AEDs, and full-scale IQ less than 70 are independent risk factors for SUDEP. Tonic-clonic seizure frequency may be a risk factor, but only in women. The presence of cerebral structural lesions was not found to be a risk factor for SUDEP (167), and this phenomenon has not been described among patients with PTE.

In summary, sequelae associated with isolated LPTS are comparable to those found in any seizure. Isolated or infrequent late seizure episodes are generally associated with relatively little risk. Increasing frequency and severity of seizure disorders, including status epilepticus, carry greater associated risks of increased morbidity or mortality, and worsened cognitive and functional prognosis.

## **POST-TRAUMATIC EPILEPTOGENESIS**

### **Epileptogenesis**

Epileptogenesis refers to the dynamic process underlying the appearance and natural history of epilepsy (9). For decades, physicians treating patients with TBI have sought to prevent the appearance of PTS by interrupting the process of the development of seizures through the prophylactic administration of AEDs. However, the pathophysiologic mechanisms involved in acquired epileptogenesis are not well understood, though they

clearly involve multiple pathways at the molecular and cellular level, as well as changes in neural networks that result in the appearance of spontaneous seizures (168). This limited understanding of the pathophysiology of acquired epileptogenesis has probably influenced the failures encountered with clinical trials of AED prophylaxis (169), discussed later in this chapter. Propelled by insights into the molecular genetics of epilepsy (170), the topic of acquired epileptogenesis is attracting increasing scientific investigation.

Aside from careful observations derived from clinical, electrographic, and neuroimaging studies among human subjects (171), much of what is known or postulated regarding acquired epileptogenesis has been derived from studying pathological specimens from surgical patients with epilepsy, as well as a large number of animal models of epilepsy (168, 171–174). These animal epilepsy models simulate human epilepsy, and provide a system for studying mechanisms that account for the characteristics of acquired epilepsy in humans (168). Such characteristics include the presence of a “latent” period between time of injury and recurrent seizure onset (171), as demonstrated in the kindling model of epilepsy, or the propensity for seizure occurrence with specific characteristics of TBI (175), as found in patients with hemorrhagic contusions and modeled in the ferric chloride model. Indeed, the presence of an unambiguous stimulus (TBI) for later appearance of epilepsy in patients with clearly identified risk factors has prompted great interest in post-traumatic epilepsy and epileptogenesis as an archetypal model for remote symptomatic epilepsy (176). The development of relevant animal models is important, as selection of AEDs for development for marketing worldwide are primarily based on results of preclinical animal model studies (169, 177). A number of these models suggest that many AEDs have antiepileptogenic potential (168). The theoretical and clinical implications of such models in the treatment of epilepsy, including post-traumatic epilepsy and epileptogenesis, have been reviewed elsewhere (155, 168, 171, 175, 177, 178). In the discussion that follows, animal models of epilepsy with historic relevance to post-traumatic epileptogenesis are followed by a review of more recent studies addressing this issue.

### **Ferric Chloride Model**

Initially described by Willmore in 1978, the iron or ferric chloride model is the first considered to reflect mechanisms responsible for post-traumatic epilepsy in humans. Specifically, it is felt to model pathophysiologic processes resulting from a cortical contusion / focal neocortical injury. It is of theoretical interest because cortical deposits of hemosiderin may be important in the development of recurrent PTS (179). Patients with cerebral injuries

characterized by contact of blood and cortical tissue manifest an increased incidence of PTS (180). Contusion or cortical laceration causes extravasation of red blood cells, with hemolysis and deposition of hemoglobin. Willmore demonstrated that recurrent focal epileptiform discharges could result from cortical injection of ferrous or ferric chloride (179). It is felt that the iron salts and hemoglobin in neural tissue may contribute to epileptogenesis by initiating lipid peroxidation, damaging cell membranes and inhibiting neuronal Na-K ATPase (174).

### Kindling Models

The kindling model of epilepsy is arguably the most recognized animal model of epileptogenesis (173, 181). When initially described (182), brief trains of weak electrical stimulation were applied to susceptible areas of rodent brains, until a seizure was observed. When continued over a prolonged period of time, progressively less stimulation was required to induce the seizures, and spontaneous seizures eventually appeared. Once established, this enhanced sensitivity to electrical stimulation appears to be permanent for the life of the animal. Here, epileptogenesis is triggered by the kindling paradigm. The relevance of kindling to remote symptomatic epilepsy derives from the hypothesis that other stimuli, such as subclinical seizures or structural brain lesions, may trigger epileptogenesis (183).

Agents that retard or abort the kindling process are considered "antiepileptogenic," whereas those that merely suppress or block seizures in fully "kindled" animals are "anticonvulsant." Such studies have demonstrated that PHT (184) and CBZ (185, 186) have anticonvulsant effects but lack antiepileptogenic action. By contrast, studies that examined the effects of GABAergic drugs, including VPA, DZP, and PB, on kindling have shown that they demonstrate antiepileptogenic properties (168, 184, 187, 188). Among the newer AEDs, TGB and LEV show antiepileptogenic action (168) in kindling models. In contrast, TPM (168) and LTG show limited antiepileptogenic activity in kindling (189, 190, 191) and rodent status epilepticus models (192). Retardation of kindled seizures appears to outlast the period of exposure to antiepileptogenic drugs, suggesting that they were not simply masking seizure expression.

Several notable limitations exist with the kindling model. For example, the original kindling studies were performed on rats. Subsequently this phenomenon was demonstrated in rabbits, cats, and later, genetically-seizure-predisposed primates (184). Since neuroanatomical structural differences between species imply functional differences, it is not surprising that animal kindling models demonstrate significant phylogenetic variability in expression (193). Further, despite the efficacy of some compounds on the kindling model, none of them has had

an indisputable antiepileptogenic action in animal models with spontaneous seizures (176) or in humans (168). Also, no disease-modifying effects have been described (192). Thus, the extent of this model's relevance to investigations of human PTE is considered controversial (181).

### Recent Studies of Post-traumatic Epileptogenesis

#### *Fluid Percussion Injury Model of Post-traumatic Epilepsy*

In 2004, D'Ambrosio and colleagues described the results of a series of experiments that demonstrate, perhaps for the first time, reproduction of post-traumatic epilepsy induced by a single episode of lateral fluid percussion injury (194), a clinically-relevant model of nonpenetrating TBI (195). Prior studies of experimental TBI (including those incorporating fluid-percussion experimental injury [196]) describe acute seizures (197), and hippocampal hyperexcitability to electrical stimulation (196, 198) or exposure to proconvulsant agents (199). However, spontaneous chronic seizures, the hallmark of epilepsy, has not been described (194). Moreover, while neocortical epileptic foci commonly develop in humans following TBI (38), changes in neocortical excitability have not been studied in rat models of nonpenetrating TBI, which have focused on the hippocampus (194). To date, investigation of neocortical pathophysiology in PTE has been limited to two approaches: the first involves studying neocortical islands isolated by undercuts from the surrounding grey matter, and the second involves chronic neocortical implantation of ferrous chloride (179, 194). Both models bear limited resemblance to the human post-traumatic condition, however, as they lack its unique focal and diffuse mechanical and hemorrhagic components (194). These limitations, in turn, potentially influence the relevance of these models to mechanisms of human post-traumatic epileptogenesis and subsequent therapies that can be translated to human PTE (194).

The study's main findings demonstrate that a single episode of fluid percussion injury is sufficient to cause PTE in the rat. The characteristics of PTE appeared comparable to those of human PTE, as seizure manifestations emerged after a latent period, and were partial in onset after a focal injury. Moreover, epileptiform activity is first detected in the neocortex at the site of injury, which electrophysiologic studies demonstrate is chronically hyperexcitable after fluid percussion injury. Finally, post-mortem pathological examination reveals that intense glial reactivity is observed at the site of injury. In summary, the clinical, electrophysiological, and structural changes of severe lateral fluid percussion injury appear to

parallel changes seen after neocortical injury in human PTE (194).

### *Synaptic Plasticity*

During recent years, a large (and increasing) number of studies demonstrate the ability of the brain to adapt to injury with changes in functional, and structural reorganization (198, 201, 202). These reorganizational changes, termed plasticity, may serve an adaptive role in development and recovery (200, 203), or a maladaptive role when they contribute to disorders such as epilepsy (203–206). Pathological studies of TBI reveal that compensatory collateral axonal sprouting occurs following brain injury (207) and may be a mechanism of importance in functional neurological recovery (200, 208). Under certain circumstances, however, collateral sprouting may give rise to the development of seizure foci (209) or the spread of epilepsy from a primary focus to synaptically-related brain regions (206). Additional excitatory synaptic contacts on cell somata could produce a marked increase in cell excitability, particularly if the new excitatory synapses replaced inhibitory ones (209). If the induced alterations in connectivity increase excitability, neural pathways could become progressively susceptible to epileptic events, and may contribute to the subsequent development of seizures (210).

While sprouting and subsequent formation of new synaptic connections has been proposed as a post-traumatic epileptogenic mechanism, it is not likely to be the only pathway to neuronal hyperexcitability (178). Postinjury development of neuronal hyperexcitability may be the result of three general types of plastic change: a) alterations in intrinsic membrane properties, b) changes in synaptic connectivity, and c) modifications of receptors and receptor subunits (178, 211). Direct axonal injury may render surviving neurons more excitable through alterations in intrinsic membrane properties. Loss of afferents can induce sprouting of axons, leading to hyperexcitability by increasing recurrent cortical pathways (178).

If the aforementioned models are important mechanisms common to both “adaptive plasticity” after TBI and “maladaptive plasticity” in PTS, potentially significant implications follow. Specifically, AEDs whose potential effects are exerted by preventing the development of compensatory excitatory neural pathways, i.e. a seizure focus, may concurrently retard neurological recovery through a similar mechanism of action (212). Moreover, since PTS occur among a minority of all patients with TBI, including severe TBI, AED therapy broadly directed against subclinical seizure activity among all TBI patients during recovery may be more detrimental to neurological and functional outcome than either seizures alone or initiation of AED therapy after seizure onset.

## **“ASYMPTOMATIC” MANAGEMENT OF POST-TRAUMATIC SEIZURES & EPILEPSY: PREVENTION, PROPHYLAXIS & PRACTICE GUIDELINES**

The term prophylaxis has been defined as “specific measures taken to prevent disease in an individual . . .” (213). In the context of PTS, the term applies to AED treatment administered to patients who have not manifested seizures. Several justifications can be proposed for prophylaxis of PTS. First, AEDs might prevent PTS at a time when they potentially pose the greatest risk of secondary injury, such as seizure-induced elevations in intracranial pressure (214). Second, seizure prevention may help avoid loss of employment, loss of driving privileges, or accidental injury (214). Third, there may exist concern over the medicolegal implications of negligent treatment if PTS appear. Finally, there exists the possibility that administration of AEDs may alter or arrest epileptogenesis. Thus far, however, animal and human studies fail to provide evidence that AED therapy prevents the development of the post-traumatic seizure focus (168), or alters the course of seizure recurrence aside from suppression of the seizure focus (177).

### **Identification of the “High-Risk” Patient**

Methods have been proposed to improve identification of those patients at risk for PTS development, and therefore those most to gain from its prevention or potential recurrence. These include assessment of the clinical characteristics of the patient, the injury, as well as information yielded by neuroimaging and electrophysiologic assessment techniques (Table 26-2).

#### *Patient Characteristics*

Age, history of alcohol abuse, and family history represent the patient characteristics most frequently cited as factors influencing subsequent seizure risk. Patients with histories of alcohol abuse, particularly chronic alcoholism, demonstrate an increased risk of early (132) and late seizure development (93, 115, 117, 121, 122, 124, 216, 220) and recurrence (41) following TBI. Few data exist regarding PTS risk associated with low levels of alcohol use, either before or after TBI. Patient age appears to exert a strong influence on PTS risk (43, 102, 104, 122). Children demonstrate markedly lower risk for LPTS, and considerably higher risk for IPTS and EPTS, when compared with adult patients with comparable injury severity. Some studies suggest that age at onset of injury (64) or seizures (221) may influence susceptibility to seizures later in life.

Some authors note a modestly increased incidence of PTS among patients with nonpenetrating TBI and a family history of seizures (4, 93, 116, 216). This has not

**TABLE 26-2**  
**Risk Factors for Late Post-traumatic Seizures**

RISK FACTOR	REFERENCE
<b>Patient Characteristics</b>	
Age	43, 102, 104, 122
Alcohol use	93, 115, 117, 121, 215
Family history	4, 93, 116, 216
APOE e allele	217
<b>Injury Characteristics</b>	
Bone/metal fragments	47, 88, 96,
Depressed skull fracture	4, 43, 94, 129
Focal contusions/injury	39, 46, 111, 113, 115, 218
Focal neurological deficits	4, 46, 47
Lesion location	46, 93, 157, 219
Dural penetration	47, 61, 93, 113, 219
Intracranial hemorrhage	43, 113, 117, 125, 218, 219
Injury severity	4, 47, 93, 97, 101, 102, 125, 219
Focal hypoperfusion	125
<b>Other</b>	
Early post-traumatic seizures	4, 47, 113, 115, 219

been consistently observed (47, 98, 222), suggesting that the influence of a family history of seizures appears weak when compared to the effects of extensive cerebral trauma (47). However, Diaz-Arrastia and colleagues recently noted that inheritance of the apolipoprotein (APOE) εε allele was significantly associated with development of late seizures, but not poorer outcome, after moderate and severe TBI (217). If such findings are replicated, genetic influence may ultimately be shown to have an important role in post-traumatic epileptogenesis.

### *Injury Characteristics*

Certain injury characteristics demonstrate an increased likelihood of resulting in recurrent, late PTS. Virtually uniform agreement exists regarding observations of markedly increased seizure risk among patients with PTBI (41, 47, 88, 90, 91–93, 97). Blood appears to demonstrate an extremely irritating effect on cortical neurons, as demonstrated by increased seizure incidence among TBI patients with intracranial bleeding, (4, 41, 43, 47, 102, 112, 116, 117, 121, 124, 218, 219) particularly with subdural hematoma (113, 219). Increased extent of PTBI (47, 92, 166); and severity of nonpenetrating TBI (41, 43, 91, 100, 126, 128), as evidenced by prolonged duration of post-traumatic amnesia (4, 41, 93, 102, 112, 114, 127), prolonged duration to follow commands (219), lower GCS (4, 101, 102, 219) or impairment of consciousness (114, 117, 124, 127), are prominently associated with increased seizure risk.

General agreement exists regarding observations of increased PTS risk in patients with TBI characterized by focal neurologic deficits (4, 41, 47, 91, 95, 97, 108, 109, 117, 124), depressed skull fractures (4, 93, 94, 112, 129), cerebral contusions (39, 46, 100, 104, 109, 110, 115, 218), and retained bone or metal fragments (88, 89, 93, 97). Lesion location may affect incidence (46, 93, 95–100, 157, 219, 223), type (64), and possibly frequency (223) and treatment response (38) of PTS. The concurrent presence of multiple risk factors is consistently associated with increased seizure risk (4, 91, 117, 122, 124).

Late PTS rarely occur after mild TBI (101). Among adults, trivial blows to the head almost never result in seizures, but may occur in the presence of preexisting (224) or concurrent (123) brain lesions. In a recent multicenter study, 8% of patients with GCS scores in the mild range (13–15) developed late post-traumatic seizures within 24 months; all had CT-scan evidence of contusion or intracranial hemorrhage (113). Despite their rarity, PTS and even recurrent PTS *do* occur after mild TBI, but their presence in the adult patient should prompt an investigation for a precipitating cause, such as an intracranial mass lesion. Moreover, frequent LPTS after mild TBI should also prompt careful evaluation for NES (59).

### *Electroencephalography (EEG)*

The utility of the interictal EEG as an objective predictor of subsequent PTS appears limited (115, 126, 225, 226). It is frequently abnormal in patients with TBI, both with and without PTS (46, 218, 227, 228), reflecting the severity of brain damage sustained (46, 226). Sleep-deprivation activation procedures similarly do not appear to differentiate between patients with and without PTS (229). The rare change of focal slow wave activity to focal spike discharges, particularly during the first month postinjury (100), or persistence of focal spike or sharp wave discharges may be suggestive of increased seizure risk (121, 225, 228). However, such discharges may be observed on the EEG of non-epileptic patients (218, 230). Conversely, a normal EEG may precede PTS onset (225–227, 231), though this finding is more frequently associated with a favorable prognosis (121, 218). EEG findings should be evaluated in context with other clinical risk factors when assessing the likelihood of PTS onset.

The EEG provides valuable information in focus localization, seizure persistence, and severity prognostication once PTS have been observed (89, 225, 232). In addition, the EEG may identify the presence of nonconvulsive seizures among patients with impaired consciousness, particularly early after severe TBI (49). The utility of the EEG in predicting PTS recurrence following a seizure-free period has not been established.

In the neurorehabilitation setting, we believe that the EEG is potentially helpful when considering the continuation of AED therapy in patients with a history of EPTS.

### AED Prophylaxis Clinical Trials and Guidelines

Encouraged by animal studies suggesting that anticonvulsants may prevent the development of epileptic foci in animals, a number of studies have been published addressing the efficacy of AED prophylaxis in TBI. These studies have been extensively reviewed elsewhere (233), and their relevant findings and conclusions summarized here. These clinical trials and literature reviews have also served as a basis for practice management guidelines addressing AED prophylaxis of early and late seizures (2, 234).

Retrospective studies and nonrandomized open trials involving human subjects appeared first in the scientific literature (92, 115, 121, 133, 235–240) with generally favorable results (236–240). Decidedly unimpressive results were observed among prospective investigations (124, 138, 218, 220, 241–245) of chronic prophylaxis for late PTS. Indeed, published randomized, controlled prospective investigations almost uniformly fail to substantiate evidence of efficacy for CBZ (218), PHT (138, 241, 242, 244, 245), PB (124), or VPA prophylaxis (243) of late PTS. In four of these trials, the incidence of PTS was actually higher among the PHT-treated groups (138, 241, 244). Meta-analyses of these trials indicate that AED prophylaxis is not accompanied by a reduction in LPTS, (168, 242, 246–248), mortality, or neurological disability (246, 248).

In contrast, AED prophylaxis consistently reduces the incidence of early PTS (138, 218, 220, 249). As in some of the studies cited previously, however, there is no clinical evidence that AED prophylaxis of early seizures reduces the occurrence of LPTS, or has any effect on death or neurological disability (248). Most published trials lack sufficient numbers of patients with PTBI to conclude whether AED prophylaxis exerts a favorable or adverse influence on seizure incidence in this high-risk subset of TBI patients (250).

While disappointing, treatment failure among trials conducted thus far should not imply that future trials are similarly destined to fail. Different approaches are currently under investigation (251). These include: 1) the use of available AEDs that have not been previously studied for prophylaxis of PTE, such as MgSO<sub>4</sub>; 2) different timing of administration (e.g. <12h postinjury) with presently-available AEDs (251); and 3) development and investigation of future AED's, preferably with demonstrated efficacy in a relevant animal model of human PTE.

Table 26-3 summarizes the practice management guidelines of four medical societies that have published guidelines pertinent to AED prophylaxis of PTS (2, 5, 234, 250). These include the Brain Injury Special Interest Group of the American Academy of Physical Medicine and Rehabilitation (BI-SIG) (2), the American Academy of Neurology (AAN) (5), the Brain Trauma Foundation ([BTF] in conjunction with the Joint Section on Neurotrauma and Critical Care) (234), and the Penetrating TBI Committee (250). The guidelines of the BI-SIG, AAN, and BTF are all very similar, and primarily address non-penetrating TBI in adults (2, 5). The guidelines of the Penetrating TBI Committee specifically

**TABLE 26-3**  
*Practice Management Guidelines for AED Prophylaxis of PTS*

PATIENT POPULATION	SEIZURE TYPE	RECOMMENDATION	DEGREE OF CERTAINTY (252)
<b>Nonpenetrating TBI (High-risk)</b>	Late PTS (without EPTS)	Not recommended	Standard (2, 23) "Level B" (5)
<b>Penetrating TBI</b>	Late PTS (without EPTS)	Not recommended (2, 250) (No specific opinion for PTBI [5, 234])	Option (2, 250)
<b>Penetrating TBI or high-risk nonpenetrating TBI</b>	Early PTS	May be used	"Level A" (5) Option (2, 234)

Degree of Certainty-strength of recommendations: **Standards** refer to generally accepted principles for patient management that reflect a high degree of clinical certainty (i.e., based on class I evidence or, when circumstances preclude randomized clinical trials, overwhelming evidence from class II studies that directly addresses the question at hand or from decision analysis that directly addresses all the issues). **Guidelines** refer to recommendations for patient management that may identify a particular strategy or range of management strategies and that reflect moderate clinical certainty (i.e., based on class II evidence that directly addresses the issue, decision analysis that directly addresses the issue, or strong consensus of class III evidence). **Options** refer to strategies for patient management for which there is unclear clinical certainty (i.e., based on inconclusive or conflicting evidence or opinion) (252).

address prophylaxis with penetrating TBI, and conclude that AED prophylaxis for LPTS appears unjustified (250).

### MANAGEMENT OF POST-TRAUMATIC SEIZURES AND EPILEPSY

It is beyond the practical scope of this review to critically examine the breadth of literature pertinent to the treatment of all patients with epilepsy, and the reader is referred to textbooks that serve this role (253, 254). Nevertheless, treatment issues that are particularly germane to patients with TBI and recurrent PTS will be briefly reviewed. In the discussion that follows, the authors' clinical experience will be incorporated into the literature review extrapolated from other epileptic populations when addressing symptomatic management of patients with PTS/PTE.

#### Diagnosis

An initial step in the management of suspected seizures is establishing whether or not a seizure disorder indeed exists (61). In light of the social, economic, and medical implications that accompany the diagnosis of an epileptic disorder, errors need to be avoided. In many cases, a diagnosis can be reliably made from clinical observations of seizure phenomena, particularly those noted by experienced staff in the hospital setting. Classification of the observed seizures is similarly important, as categorization can have significant prognostic and therapeutic implications.

There are situations, however, where the diverse or subtle clinical presentations of PTS complicate diagnosis. As noted earlier, epileptic manifestations (particularly those of CPS) may not be recognized in patients with significant cognitive and behavioral dysfunction. Alternatively, nonepileptic phenomena such as NES, myoclonus, or syncopal episodes may be mistaken for PTS. Clinical observations alone may thus be insufficient to render or rule out a diagnosis of PTS, prompting the use of other diagnostic options (48).

The EEG is the single most informative laboratory test for the diagnosis of epileptic disorders (255–257) and should be obtained in any patient with suspected PTS. The EEG may assist in assessing the likelihood of an underlying epileptic condition when correlated with the clinical diagnosis (258), or in localization of the seizure focus (255). Although interictal epileptiform activity is apparent in only approximately 50% of single awake recordings in adults with epilepsy, this proportion rises to approximately 80–85% if sleep is included. Two recordings obtained while the patient is awake will demonstrate epileptiform activity in 85% of individuals with epilepsy, and this rises to 92% of persons within four recordings (255). In patients who manifest only generalized seizures,

interictal discharges are bilateral, symmetrical and synchronous, generally of greatest amplitude over the frontal regions but sometimes located posteriorly. In patients with partial seizures, discharge topography will more or less closely correspond to that of the focus from which seizures arise. These focal interictal discharges may spread, producing secondarily generalized spike-and-slow-wave activity. If the generalization is rapid, the focal onset may be difficult to detect (255).

There exist limitations in the diagnostic sensitivity of the standard interictal EEG, however, and absence of EEG abnormalities does not exclude the presence of a seizure disorder (255). Postictal PRL measurement may be useful in some of these patients, as significant elevations in serum PRL levels reliably occur within 20–40 minutes following GTC seizures (259) and many CPS (259). PRL elevations are typically not observed after SPS (260), CPS of frontal lobe origin (261), or after 30 minutes in most patients with NES (57, 58, 260). Significant PRL elevation occurring after a possible PTS episode may help confirm clinical suspicion of an underlying epileptic disorder (262). Given the significant diurnal variation in serum PRL levels, however, it is often prudent to obtain a baseline value for comparison, drawn at the same time of day as the postictal specimen, within a few days.

When initial standard evaluations fail to resolve the clinical diagnosis, long-term EEG monitoring techniques, including ambulatory EEG monitoring (263, 264) and/or inpatient VEEG telemetry (255, 265) are effective and clinically valuable (48). Ambulatory EEG monitoring offers an intermediate-level option for recording while the patient conducts normal activities at home, work, or school (9, 263, 264). It is most useful for investigating the patient in a natural environment; for example, to test the claim that a patient has seizures at home which are not observed in hospital (255). A patient or observer log is maintained to identify the times and descriptions of behavioral episodes suspected of representing seizure activity (9). Ambulatory monitoring has been transformed by the recent development of recorders using solid-state memory or removable miniature digital discs (255). Ambulatory monitoring is usually performed without simultaneous video registration, however, and thus EEG telemetry with video monitoring provides the best opportunity to obtain an artifact-free ictal EEG while observing and evaluating associated clinical behavior (265). Concurrent computerized automatic seizure detection often identifies important events, particularly at night, that are not reported by the patient or nursing staff. Definitive diagnosis requires recorded examples of all seizure types experienced by the patient (255). Conversely, an absence of discharges during prolonged monitoring, particularly in a patient with frequent



seizures, may serve to cast doubt on the diagnosis of epilepsy (255).

Hudak et al. recently described the utility of prolonged VEEG monitoring in the clinical management of paroxysmal behaviors in TBI survivors (48). In this retrospective record review, 127 patients with a documented history of moderate-to-severe brain injury preceding onset of frequent, disabling paroxysmal behaviors were evaluated in an epilepsy monitoring unit for management of medically intractable epilepsy. VEEG monitoring was conducted for an average of 4.6 days. AED administration was suspended during the assessment period. Monitoring was successful in establishing a diagnosis in 82% of the cases referred. Sixty-two percent of the evaluated patients had focal seizures, 6% had generalized seizures and 33% had psychogenic NES. The authors concluded that VEEG is a useful procedure in the evaluation of TBI survivors with paroxysmal behaviors suggestive of epilepsy, and that the yield of diagnoses that may alter treatment is substantial (48).

### Treatment and Selection of the AED

While broad agreement exists regarding the appropriateness of AED treatment among patients who manifest two or more seizures, considerable debate remains concerning the benefits of treatment in reducing recurrence risk following a first seizure (266, 267). Overall, about 33 percent of patients with a first unprovoked seizure can be expected to have a second within the subsequent three to five years. This risk varies considerably, however, depending on clinical characteristics of the patient (268). Increased risk is observed among patients with remote symptomatic epilepsy (268, 269, 270). Approximately 44–48% percent of patients with a first remote symptomatic seizure will experience a second seizure in the next three to five years (268, 269). Of the patients with a second seizure, almost 87% will experience a third seizure at five years (268). Seizures occurring immediately following an acute precipitant or injury to the brain carry a lower risk of recurrence than a late seizure (271).

Treatment after first seizure has been advocated, though few randomized clinical trials have been conducted to establish the efficacy of this practice. One randomized multicenter clinical trial concluded that treatment of the first seizure with antiepileptic drugs leads to a significant reduction of relapse risk. The authors added, however, that the decision to start treatment in a patient with a first seizure must balance that patients risk of relapse, the benefits of avoiding the consequences of a second seizure, and the risk of AED toxicity (272).

Once a decision has been reached that pharmacological treatment of a patient with PTS is indicated, a primary goal is to attain control of seizures with one medication (9, 273). The decision of which specific agent to

use will reflect the type of post-traumatic seizure, the route and frequency of drug administration, as well as the anticipated and realized adverse effects. Among patients with symptomatic localization-related epilepsy (273), including patients with TBI who manifest seizures of partial onset, extended release CBZ remains a commonly preferred drug (233, 273, 274). Patients with tonic-clonic seizures of generalized, secondarily generalized, or multifocal onset respond well to VPA (273–275). CBZ (275) and PHT (275, 276) are also effective anticonvulsants for GTC seizures. While generally effective for seizure control of tonic-clonic seizures (9, 276), the utility of PB is severely limited by prominent adverse effects on cognition and behavior (277), and is rarely used in current practice (278).

Anecdotal evidence suggests that neurologists and physiatrists increasingly employ newer “second generation” AEDs in symptomatic management of selected patients with PTE. Unfortunately, there currently exists little scientific data, specific to PTE, that support (or refute) the benefits of this practice. For example, a recent PUBMED literature search (September 2004), cross-referencing the terms “post-traumatic seizures” or “post-traumatic epilepsy” with key words of the newer AEDs, including “lamotrigine”, “topiramate”, “oxcarbazepine”, “levetiracetam”, or “tiagabine”, failed to yield a single reference. Presently, extrapolation from scientific literature derived from other patient populations, particularly those with remote symptomatic epilepsy, and evolving clinical experience are all that exist to guide clinical practice with newer AEDs for patients with PTE.

Fortunately, two expert consensus panels recently address the use of the newer AEDs as initial monotherapy (273, 279), including patients with symptomatic localization-related epilepsy (SLRE) and symptomatic generalized epilepsy (SGE)(273). The Quality Standards and the Therapeutics and Technology Assessment Subcommittees of the American Academy of Neurology published a practice parameter summarizing an evidence-based assessment regarding the efficacy, tolerability, and safety of seven new AEDs in the management of new onset partial or generalized epilepsy, including GBP, LTG, TPM, TGB, OXC, LEV and ZNS (279). They found evidence that GBP, LTG, TPM, and OXC are effective as monotherapy in newly diagnosed adolescents and adults with either partial or mixed seizure disorders, but not generalized epilepsy syndromes. No specific guidelines were provided regarding AED use in remote symptomatic epilepsy or PTE (279). Karczeski et al. employed an “expert consensus method” to survey epilepsy specialists (273) regarding AED preference in specific clinical scenarios. The survey revealed a preference for CBZ as the initial AED for management of symptomatic epilepsies. Besides CBZ, PHT, OXC and LTG were also cited as initial first line agents for SLRE manifested by simple partial seizures or complex

partial seizures. For management of SLRE with secondarily generalized seizures, PHT, OXC, LTG, and VPA were identified as initial first line AEDs (273). A limitation of this consensus statement (273) is that it does not address the place of ZNS or LEV in the clinical armamentarium, as these agents were not in wide use at the time the survey data were obtained.

### Adverse Effects of AED Therapy

Antiepileptic drugs commonly employed in the treatment of PTS may be associated with significant idiosyncratic and dose-related adverse drug reactions (279, 280, 281), requiring their discontinuation or substitution in as many as 20–30% of patients (282, 283). These include hematologic, dermatologic, hepatic, neurologic, endocrinologic, urologic, and teratogenic adverse effects (279, 284, 285). Transient or persistent leukopenia and thrombocytopenia may be observed in patients taking PHT and CBZ, though idiosyncratic aplastic anemia is extremely rare. Rashes are occasionally encountered with many AEDs and severe dermatologic reactions more rarely noted with LTG and PHT (279, 280). Hirsutism and gingival hyperplasia may be problematic in patients treated with PHT (280). Weight gain has been associated with VPA and GBP treatment, and weight loss reported with ZNS and TPM (275, 279). Mild and transient elevations of hepatic enzymes, up to two to three times normal in some cases, are reported to occur in patients receiving PHT, CBZ, and VPA, (286). Frequent and rigorous routine laboratory monitoring regimens, however, aside from baseline determination of hematologic and hepatic function or closer observation of noted abnormalities, are unjustified for most AEDs (with the notable exception of FBM). These typically do not provide meaningful protection from rare and potentially life-threatening manifestations (287, 288). Appropriate counseling for the patient, family, and/or caregivers regarding potential complications and symptoms that might herald an adverse event is far more useful and important (288).

Cognitive effects of AEDs warrant particular attention in the patient with TBI. Newer AEDs demonstrate superior cognitive adverse effect profiles and tolerability when compared with older agents (302, 303, 304). In contrast, older AEDs, particularly PB, PHT and CBZ, significantly impair memory performance in double-blind crossover trials among healthy adults (289). Patients with severe TBI already have significant cognitive impairment. Antiepileptic drugs may exert independent and additional adverse cognitive effects on the patient with TBI who is receiving chronic therapy (290). Among patients with severe TBI participating in the landmark prophylaxis trial of Temkin et al. (138), a significantly greater proportion (78%) of individuals treated with PHT demonstrated cognitive impairment sufficient to preclude testing at one

month postinjury. This was observed in only 47% of corresponding patients treated with placebo (290).

Among older established AEDs, most studies demonstrate no comparative advantage in cognitive adverse effect profile between CBZ, PHT, or VPA, though few include subjects with TBI (291–294). Smith (294) found no significant difference on cognitive testing results among patients randomized to withdrawal from PHT and CBZ prophylaxis. Only 13 of the 82 studied patients sustained severe TBI, however, with the remainder receiving prophylaxis following craniotomy or mild/moderate TBI. There remains considerable evidence suggesting that PHT provides a relatively unfavorable cognitive side effect profile among patients with severe TBI (290, 291). Patients randomized to receive 6 months of VPA for prophylaxis of LPTS following severe TBI demonstrated no evidence of adverse cognitive effects when compared with those receiving 1 week of PHT (291). In contrast, an earlier study among comparably injured patients receiving PHT prophylaxis yielded unequivocal evidence of cognitive impairment among AED-treated patients (290).

While attention regarding adverse drug effects frequently focuses upon observable phenomena, such as lethargy, the influence of AED therapy upon the course of postinjury neurologic recovery also warrants consideration (295). Specifically, certain drugs, including AEDs, clearly impair recovery after brain injury in laboratory animals (296–298). Schallert et al. (298) demonstrated that diazepam administered to rats within 12 hours of neocortical damage delayed recovery indefinitely, whereas delayed administration of diazepam resulted in only transient reinstatement of neurologic deficit (298). Brailowsky observed that PHT increased the severity of cannula-induced cortical hemiplegia in rats, though motor impairment was not seen when administered to the animals after their hemiplegic syndrome had cleared (296). These findings suggest that AED administration with diazepam or PHT during certain critical periods following brain injury may exert a deleterious effect upon subsequent neurologic recovery.

In summary, dose-related and idiosyncratic adverse effects occur among a substantial subset of treated patients, particularly with older AEDs. Cognitive adverse effects may be particularly problematic, particularly with the older established agents, impacting upon long-term tolerability. The cited studies serve as a reminder that decisions regarding chronic AED treatment, and particularly prophylaxis, cannot be considered solely on the merits of effectiveness in seizure prevention. Rather, consideration must also be given to potentially significant adverse effects and toxicities of the AED regimen.

### AED Substitution

Neurosurgeons and neurologists have preferred PHT for prophylaxis (299, 300) and symptomatic AED treatment,

primarily because of its availability in parenteral forms that can be administered in the acute setting, where seizures are more likely to occur. Since the publication of prophylaxis guidelines (2, 5, 234), however, we have observed a clear trend towards less frequent use of AED prophylaxis. In addition, among patients receiving symptomatic AED treatment, PB use is rare, with PHT remaining the most commonly observed for use in acute care settings AED for initial symptomatic management. These patients are commonly maintained on the chosen AED until a satisfactory seizure-free duration has passed. AED substitution has previously been usually reserved for failure of seizure control or the manifestation of significant drug reactions (9). As mentioned earlier, selection of a newer AED as initial monotherapy is likely to improve tolerability, particularly with cognitive adverse effects, while maintaining comparable efficacy. For similar reasons, many neurorehabilitation specialists consider substitution of PHT monotherapy for other less cognitively-impairing medications, such as LTG, as clinical circumstances allow.

When substituting an AED for another drug, clinically effective levels of the latter AED should be attained prior to discontinuation of the former drug (9). Among the newer AEDs, serum levels are not commonly obtained, although these are available at reference laboratories. Once appropriate and effective doses of the new drug are achieved, a gradual taper of the former drug ensues. At one time, CBZ was the most common AED employed for substitution instead of PHT in our center. More recently, however, we use LTG as slow add-on therapy (usually added to PHT), followed by gradual withdrawal of PHT after maintenance of seizure control and effective doses of LTG (approximately 4–500mg /day). Our preference for LTG derives from a clearly favorable cognitive adverse effect profile, particularly when compared with either PHT or CBZ (301). Among patients requiring more rapid additional seizure control, LTG is not a therapeutic option, due to the increased danger of serious rash or Stevens-Johnson syndrome (305) associated with rapid dose increases. Instead, we employ VPA, as it is effective for both generalized and partial seizures (275), it demonstrates generally favorable tolerability among patients with TBI (291), and it is available in parenteral and once-daily oral formulations. VPA may also be a practical choice among patients with PTE that are also demonstrating post-traumatic mood lability and irritability. We are aware of colleagues that favor LEV as a preferred AED for substitution among patients with TBI, citing its ability to be rapidly titrated to effective dose range (306) as well as its tolerability. However, anecdotal reports of a lack of persistent antiepileptic effect, and documented psychiatric adverse effects (307), may limit the utility of this agent in some patients.

### **Duration of AED therapy**

No clinical studies specifically address the duration of AED therapy for patients with recurrent LPTS. In general, it is reasonable to consider AED withdrawal from patients with epilepsy after a 2-year period free of seizures (308). Reported rates of relapse vary considerably, and reflect the type of seizure disorder being treated (9). The risk of seizure recurrence under a policy of slow AED withdrawal is still substantial when compared with a policy of continued treatment, particularly during the first year of withdrawal (309). Increased risk of recurrence has been reported among patients with a history of more frequent seizures, treatment with more than one AED, a history of GTC seizures (309), and abnormal or epileptiform discharges on pre-withdrawal EEGs (308, 310). Among patients for whom the risk of relapse after discontinuation appears low, the psychosocial benefits of discontinuation may be considerable (311). There is no consensus regarding the ideal period over which AEDs should be withdrawn in patients with recurrent seizures, although conservative recommendations advise a period of 12 months (9, 312). Worsening of seizures following PHT (313, 314) or CBZ (314) discontinuation is believed to reflect the loss of therapeutic drug effect rather than a withdrawal phenomenon. In contrast, withdrawal exacerbation of seizures is prominent with barbiturates (315) and benzodiazepines (316), and does not indicate that the drug was necessary for maintenance of seizure control (9).

### **Surgical Treatment of Post-traumatic Seizures**

Recent studies are providing valuable insight into the natural course of history regarding post-traumatic seizure recurrence (136). These studies identify a subset of patients remaining refractory to treatment, even with multiple AEDs. The definition of “refractory” is debatable, and there is evidence that adding a 2nd or 3rd AED may facilitate seizure remission in about one-fifth of patients that remain with seizures while taking a single AED (317). Nevertheless, for those patients who continue to experience frequent seizures despite various AED monotherapy or polytherapy combinations, surgical treatment options are increasingly available, particularly in recent years (318).

### **Surgical Resection of Epileptic Focus**

Advances in neuroimaging technology, coupled with results of recent landmark studies, have prompted a dramatic shift toward surgical treatment for certain types of medically-refractory epilepsy (217, 319). There is now growing sentiment among epilepsy specialists that surgical treatment for refractory epilepsy is seriously underutilized (319, 320). In the first randomized study comparing surgical and medical treatment for temporal lobe epilepsy,

58 percent of surgically treated patients were free of disabling seizures at one year, versus only 8 percent of those assigned to receive medical treatment (321). Significant improvements in outcome were observed in measures of quality of life as well as a trend with respect to social functioning (321). The Multicenter Study of Epilepsy Surgery similarly reported that resective surgery significantly reduced seizure recurrence after medial temporal (77% 1-year remission) and neocortical resection (56% 1-year remission) (322). In light of such findings, the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons, published a practice parameter supporting the benefits of anteromesial temporal lobe resection for disabling complex partial seizures. It further recommended referral of patients with these seizures to an epilepsy surgery center (319).

### *Surgical Excision of the Post-traumatic Seizure Focus*

Surgical excision of the seizure focus also provides an important treatment option for carefully selected patients with refractory PTE. Favorable responses, including seizure freedom have been described among selected patients with PTE treated with resective surgery (38, 140, 323). Patients with unilateral post-traumatic frontal lesions who undergo complete resection of perilesional encephalomalacia /gliosis and adjacent electrophysiologically abnormal tissue respond particularly well to surgery (324, 325). The cumulative experience described in published studies, however, also highlight the challenges accompanying accurate identification of the seizure focus in patients with severe TBI, who often demonstrate bilateral and multifocal injury (38, 64). Marks described 25 patients with PTE treated in their tertiary epilepsy center, 21 of whom were treated surgically. Seventeen of these patients were felt to have mesial temporal lobe epilepsy, and another 8 patients were judged to have neocortical epilepsy. Of the 21 patients treated with surgery, only 9 (43%) had favorable outcomes, characteristically those with well-circumscribed hippocampal or neocortical focal lesions (64). Schuh and associates reported on 102 patients who underwent anterior temporal lobectomy. A history of TBI, alone or in combination with other factors, was significantly correlated with continued seizures after surgery (326).

### *Vagus Nerve Stimulation (VNS)*

Vagus nerve stimulation (VNS) is an alternative to pharmacologic treatment of seizures in patients who have failed conventional pharmacotherapy, either due to lack of efficacy or adverse effects (327). The mechanism of action of VNS is not yet clear (328).

VNS is approved by the FDA for adjunctive treatment of intractable partial seizures in patients over

12 years old. Based on controlled, randomized trials, approximately 30% of these patients can be expected to have at least a 50% decrease in overall seizure frequency (329, 330). Efficacy in LPTS has not been specifically studied. Persistence of benefits has been demonstrated (331). While this technique is indeed invasive, no intracranial surgery is required, and surgical morbidity and mortality are limited. Adverse effects include hoarseness, cough and dysesthetic sensations in the throat (330).

While numbers of patients treated with this technique are limited compared to AED therapy, in 1999, the American Academy of Neurology Therapeutics and Technology Subcommittee classified VNS as safe and effective for intractable partial seizures, based on sufficient Class I evidence (332). At present, VNS is considered to be an appropriate therapy for patients with medically refractory epileptic seizures who are not optimal candidates for resective epilepsy surgery (327).

A potential advantage to the use of VNS in the context of LPTS is the relative absence of cognitive adverse effects. However the role of this technology in the treatment of epilepsy in the context of TBI remains to be delineated.

### **Consultation and Referral**

Guidelines for the appropriate level of primary and specialty care of patients with seizures, including recommendations for referral to specialty centers, have been published (333). In summary, the first step for individuals experiencing an initial seizure or seizures is to consult their primary-care physician in their own community. The primary physician may then choose to begin a treatment program or refer the individual to a general neurologist for consultation. In any case, if seizures continue to occur after three months, a referral to a general neurologist is indicated. When the seizures are controlled, many patients appropriately return to the care of their primary physicians, with follow-up to the neurologist as needed. If seizure control is not achieved at the end of the first year of treatment, referral to a center that offers comprehensive diagnostic and treatment services to patients with intractable seizures is indicated (326).

### **CONCLUDING STATEMENTS**

In light of the evidence previously discussed, our management approach for LPTS is presented. Patients with acute TBI who are transferred to the neurorehabilitation hospital setting receiving an AED for prophylaxis, and without reported early seizures, are gradually tapered from AEDs early in their hospital course. As mentioned previously, routine chronic AED prophylaxis of LPTS is

unjustified, and with few exceptions\* no AED therapy is provided unless late seizures are reported (2, 5). AED prophylaxis withdrawal in the hospital setting facilitates monitoring for the potentially varied manifestations of seizures. Since seizures tend to occur in the earlier postinjury period, this also helps insure the presence of trained personnel should a seizure be observed during or after AED withdrawal. We have observed that marked improvements in the cognitive status of patients frequently coincide with termination of AED prophylaxis.

If a possible late post-traumatic seizure is observed, either during the patient's hospitalization or after discharge, a search for an identifiable seizure precipitant takes place, and includes a neuroimaging study of the brain. If no obvious correctable seizure precipitant is identified, establishment of a diagnosis of seizure disorder ideally precedes initiation of AED therapy. Clinical description of the episode alone, provided by a family member or other witnesses, may be sufficiently convincing to initiate AED therapy. The patient and family are given instructions for keeping a "seizure logbook," and more frequent follow-up visits are often warranted. If a late PTS has been documented, we will typically proceed with selecting an AED for symptomatic seizure management. Most commonly, we choose between a CBZ-extended release formulation, VPA, or LTG. AED selection is influenced by the: 1) patient's cognitive and behavioral status; 2) type/manifestation of the seizure, (e.g., GTC status epilepticus versus SPS lip twitching); 3) perceived need for rapid achievement of a therapeutic dose, and 4) whether or not the patient has already been started on PHT or another AED in the emergency department. If the patient is receiving PHT and seizures are well-controlled, an alternative AED such as LTG is usually substituted at the earliest suitable point to minimize adverse side effects, particularly cognitive impairment.

For most physicians caring for patients with TBI in the rehabilitation setting, the issue of whether to institute prophylaxis of EPTS is usually moot. Nevertheless, postinjury prophylaxis of EPTS with PHT or FPT may be justified in patients with severe TBI belonging to high-risk groups. The patient is at their highest risk for seizure development, at a time when they can least afford to endure complications from a seizure. Prophylaxis may

be continued for approximately 1 week if seizures are not observed, and then tapered gradually. Again, this should take place in a setting in which close observation can be provided. The risks incurred with such a short duration of treatment currently appear minimal, and acceptable.

Insufficient data exist to definitively guide AED therapy among patients whose only manifestation of a seizure disorder are EPTS. Most published reports exclude these patients from further study, thereby losing valuable information regarding the influence of continued AED therapy on LPTS recurrence risk. Issues to consider include onset (day 1 versus day 7 or later), severity (particularly status epilepticus), recurrence frequency, and clinical risk factors for recurrence. Factors favoring continuation of AED therapy would include later time of seizure onset, documented episodes of status epilepticus, persistent epileptiform activity or electrographic seizures on EEG, multiple seizure episodes throughout the first week of injury, and the presence of multiple risk factors suggestive of high risk for LPTS occurrence, such as penetrating TBI. In contrast, it may be reasonable to consider a monitored withdrawal of AED therapy in selected patients with isolated EPTS, particularly those with IPTS. Our experience suggests that most patients with non-penetrating TBI and isolated EPTS will tolerate discontinuation of AED therapy without seizure recurrence (131, 334).

Major themes involving the symptomatic management of patients with PTS have been discussed above, and will not be repeated here. Still, important research questions remain, and involve a broad range of topics pertinent to the diagnosis and treatment of epileptic disorders. Investigation must be directed towards identifying laboratory models that reflect human response to prevention of an initial or recurrent PTS. Further study is needed to clarify the natural history of PTS, the prognostic implications of single or isolated seizures, and the effect of AED therapy upon recurrence risk. Future studies should address the comparative utility and adverse effects of symptomatic seizure treatment, including surgery, *upon adult and pediatric subjects with TBI*, and explore the potential effects of these therapies upon neurologic recovery and functional outcome.

Finally, assessment of each patient's risk and suitability for treatment must be made on an individual basis, guidelines or algorithms notwithstanding. Even with the publication of four guidelines (2, 5, 234, 250) addressing the issue of AED prophylaxis, discussion of issues related to PTS with the patient and family members is useful and important. Moreover, the clinician should be aware of the prevailing regional standards of care regarding symptomatic management. Lastly, in instances where questionable or repeated seizures occur, utilizing the assistance of neurological and neurosurgical consultants with

\*Our exceptions to this general rule include: 1) history of episodes suggestive of EPTS, especially SE; 2) anticipated intracranial surgical procedure within the next 7–14 days; 3) EEG findings consistent with epileptiform activity and/or electrographic seizures; and 4) concurrent serious medical or neurological complications, such as sepsis or hydrocephalus awaiting shunt placement; and 5) patient history of severe alcohol or substance abuse with poor family/caregiver support. (Our experience has found that number of this latter group of patients have probably experienced undiagnosed seizures or epilepsy prior to their most recent TBI.)

specific interest in the unique management issues of this patient population can be invaluable.

### Abbreviations: (For text and tables)

AED:	Antiepileptic drug
APOE:	Apolipoprotein E allele
CBZ:	Carbamazepine
CPS:	Complex partial seizure(s)
DZP:	Diazepam
EPTS:	Early post-traumatic seizure(s)
FBM:	Felbamate
FPT:	Fosphenytoin
GBP:	Gabapentin
GCS:	Glasgow Coma Scale
GOS:	Glasgow Outcome Scale
GTC:	Generalized tonic-clonic seizure(s)
IPTS:	Immediate post-traumatic seizure(s)
LEV:	Levetiracetam
LPTS:	Late post-traumatic seizure(s)
LTG:	Lamotrigine
NES:	Nonepileptic seizures
OXC:	Oxcarbazepine
PB:	Phenobarbital
PHT:	Phenytoin
PRL:	Prolactin (serum level)
PTE:	Post-traumatic epilepsy
PTBI:	Penetrating traumatic brain injury
PTS:	Post-traumatic seizure(s)
SE:	Status epilepticus
SGE:	Symptomatic generalized epilepsy
SGS:	Partial onset seizure with secondary generalization
SLRE:	Symptomatic localization-related epilepsy
SPS:	Simple partial seizure(s)
SSRI:	Selective serotonin reuptake inhibitor(s)
SUDEP:	Sudden death in epilepsy
TBI:	Traumatic brain injury
TGB:	Tiagabine
TPM:	Topiramate
VEEG:	Video-electroencephalography
VNS:	Vagus Nerve Stimulation
VPA:	Valproate
ZNS:	Zonisamide

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# 27

## Movement Disorders After TBI

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**T**rauma to the central and peripheral nervous system is an important etiologic factor in a variety of movement disorders. While it is widely accepted that traumatic brain injury may result in both transient and persistent movement disorders (1, 2), their occurrence after peripheral injury still has not become generally appreciated (3, 4). Kinetic tremors and dystonia are the best investigated posttraumatic movement disorders after severe brain injury (5–7), but many other types of hypokinetic and hyperkinetic movement disorders have been reported as sequelae of injury to the central nervous system. The manifestation of movement disorders after moderate or mild brain injury has been less well documented. The association between brain injury and Parkinson's disease (PD) is the subject of ongoing research (8, 9). Trauma as a cause for the development of movement disorders has multifaceted implications regarding medical and psychological, but also legal aspects (10–12). In some cases of posttraumatic movement disorders a definite cause-and-effect relationship is difficult to establish. This is partly due to associated circumstances, including medicolegal factors, but also because the appearance of movement disorders may be delayed and cause-and-effect relationships may not be recognized.

Posttraumatic movement disorders can lead to marked disability in the affected individual. Reviews on this subject have concentrated more on phenomenological

aspects and medical treatment options (1, 2, 13), and less on neurorehabilitation and neurosurgical options (14). Contemporary functional stereotactic surgery may provide long-term symptomatic and functional benefits in many patients with movement disorders who do not benefit sufficiently from medical treatment (15). Radiofrequency lesioning of the thalamus and pallidum was the method of choice for years for patients with disabling tremor or parkinsonism and levodopa-induced dyskinesias, but in patients with diffuse axonal injury (DAI) ablative procedures, particularly when performed bilaterally, have been frequently associated with complications such as increased dysarthria or gait disturbance. Deep brain stimulation (DBS) is used increasingly as an option in such patients. In this chapter, we review the current understanding of the role of central trauma in the development of movement disorders, their diagnosis and treatment including neurosurgical options.

### MOVEMENT DISORDERS AND BRAIN INJURY

#### Phenomenologic Classification of Movement Disorders

*Movement disorders* in the following context are understood as phenomenological entities manifested either by slowness and poverty of movement, that is hypokinesia,

by excessive, abnormal involuntary movements, that is hyperkinesia, or by other signs and symptoms that can not easily be grouped under these two categories. Note, that the term *movement disorder* is not synonymous with *motor disorder* covering also paresis, spasticity and ataxia which will not be discussed in this chapter. Also, the hypertonic postures seen in comatose patients with decorticate and decerebrate rigidity after severe head injury will not be the subject of this review. Most frequently, movement disorders are associated with dysfunction of the thalamus or the basal ganglia and their circuitry. Therefore, such disorders have also been summarized as *extrapyramidal disorders*, previously. This term, however, is not considered useful anymore, since the arbitrary concept of a pyramidal versus an extrapyramidal motor system does not adequately reflect the complexity of the organization of the motor system. In the past few years, much progress has been made in the understanding of the functional neuroanatomy, the neurochemistry, and the neurophysiology of the basal ganglia and their circuitry. These advances have had an extraordinary impact on new pharmacological treatments and the reevaluation of surgical approaches.

Many different classifications of movement disorders exist. The International Classification of Diseases Tenth Revision: Neurological Adaptation, a result of collaboration between the World Health Organization and the Movement Disorder Society has provided a classification which can be periodically revised and up-dated, and which can serve as a basis for international communication, research, and education (16). *Tremor* has been defined as a rhythmic, oscillatory movement, and it can be further divided according to the position, posture, or motor activity necessary to make it manifest (17). *Rest tremor* is seen when the body part is in complete repose. Maintenance of a posture such as holding the arms outstretched reveals *postural tremor*, whereas moving the body part from one position to another (e.g. the finger-to-nose maneuver) brings on *kinetic tremor* (termed *intention tremor* when tremor occurs only shortly before the goal of the movement is reached). *Dystonia* is characterized by involuntary, sustained, patterned muscle contractions of opposing muscles resulting in repetitive twisting movements or abnormal postures (18). Dystonic movement disorders often are misdiagnosed or they are not even recognized because the full spectrum of phenomenology has not been appreciated. Dystonia may be accompanied by tremor or rapid jerking movements. It may be present at rest, but it is usually exacerbated or elicited by voluntary activity (action dystonia). According to its distribution dystonia can be classified as focal, segmental, generalized or as hemidystonia. The term *athetosis* is used when phasic writhing dystonic movements of the extremities prevail in patients with secondary generalized dystonia. In *chorea*, rapid unpredictable movements spreading

from one muscle group to the other prevail, predominantly affecting the distal limbs. *Ballism* has been defined as continuous, non patterned, purposeless movements involving chiefly proximal portions of limbs (19). It usually presents as hemiballism and is related most frequently to lesions of the contralateral subthalamic nucleus. Experimental data suggest that chorea and ballism are parts of a continuum of movement disorders (20). Ballism, thus, can be considered a form of forceful, flinging, high-amplitude, coarse chorea. *Tics* are usually rapid jerklike movements or involuntarily produced sounds and words occurring out of a background of normal activity. Both motor and vocal tics may be categorized as simple or complex. Tics are differentiated from other movement disorders also with regard to their particular features such as the presence of premonitory feelings or sensations, variability, temporary suppressibility, and distractibility. *Myoclonus* is defined as a sudden, brief, shocklike involuntary movement that may be caused by both active muscle contraction (positive myoclonus) and inhibition of ongoing muscle activity (negative myoclonus). *Hyperreflexia* is characterized by exaggerated startle responses to sudden unexpected stimuli. *Stereotypy* is an involuntary, patterned, repetitive, continuous, coordinated, purposeless or ritualistic movement, posture, or utterance which may either be simple or complex, such as self-caressing. *Akathisia* refers to a sense of restlessness and the feeling of a need to move. *Paroxysmal dyskinesias* occur intermittently with bouts of sudden-onset, short-lived involuntary movements which may be dystonic or choreic. *Parkinsonism* is characterized by a combination of bradykinesia, rigidity, rest tremor, and postural instability. *Bradykinesia*, slowness of movement, is the clinical hallmark of hypokinetic movement disorders.

### Epidemiology of Movement Disorders Related to Brain Injury

Most posttraumatic movement disorders are due to severe brain injury. There are only few epidemiologic studies that have investigated the relative incidence of posttraumatic movement disorders. These studies yielded a wide variability ranging from 13% to 66% of patients who suffered severe brain injury (21–25). In a study on severe pediatric brain injury in Poland “extrapyramidal syndromes” were described in 18 out of 100 (18%) children (25). In another study, from Japan, 33 of 57 (58%) patients who were in a persistent vegetative state secondary to severe brain injury in motor vehicle accidents had “involuntary movements” (23). In this group palatal myoclonus and dystonia were observed most frequently. In another study of severe pediatric closed head injury, 4 out of 31 children were described to develop a “basal ganglia syndrome” (21). Exceedingly high rates of post-traumatic tremors were found in a questionnaire-based

survey, screening severely head-injured children for the presence of “significant tremor” (22). Tremors were reported in 66% of the responders to the survey (131 of 199 children). Taking into account that tremors might not have been present in cases that did not return the questionnaires the frequency of tremor in this pediatric population still was as high as at least 45%. We have analyzed the frequency of posttraumatic movement disorders in survivors of severe head injury who were admitted to a multidisciplinary trauma unit over a period of 5 years (24). This study included 398 consecutively admitted patients with a Glasgow Coma Score (GCS) of 8 or less. Follow-up was available on 221 of the 264 survivors. Overall, posttraumatic movement disorders were found in 22.6% (50 of 221 patients); they were only transient in 10.4% (23 of 50 patients), but were still present at the time of the investigation at a mean follow-up of 3.9 years in 12.2% (27 of 50 patients) (Table 27-1). Tremors were the most frequent movement disorders. Only in 5.4% of all patients, however, were the movement disorders considered disabling. The presence of generalized edema on the CT scan at admission was significantly associated with the occurrence of movement disorders. Similar

associations were detected for focal cerebral lesions, but not for subdural or epidural hematomas.

The absolute number of severe head injuries has decreased in most industrialized countries during the last two decades. Also, the management of head injury has improved considerably. It is still unclear whether these factors will translate into a lower frequency and a difference in the severity of movement disorders secondary to craniocerebral injury in the future. Different movement disorders may co-occur in a patient subsequent to severe head injury. In the study on the frequency of posttraumatic movement disorders in survivors of severe head injury mentioned above, 50 patients had a total of 59 phenomenologically distinct movement disorders (24). Treating one component with medication or surgery will not necessarily have an impact on the other. Furthermore, the co-existence of spastic hemiparesis or quadriplegia is observed frequently. In the individual patient, it may be difficult to distinguish dystonia from accompanying spasticity. It is pivotal to appreciate co-existing neurologic deficits in these patients in order to determine whether or not surgical treatment directed specifically to the movement disorder will make an impact in the patient’s overall functional disability.

Systematic study of the frequency of posttraumatic movement disorders after moderate or mild brain injury is sparse. Such associations have been documented, however, by numerous anecdotal case reports or case series. In a survey of 519 patients who suffered head injury with a GCS between 9 and 15 upon admission to the hospital, 158 patients were available for a detailed follow-up study (26). In 16 of these 158 patients (10.1%) we diagnosed a posttraumatic movement disorder. Overall, movement disorders were transient in 7.6% (12 patients) and persisted only in a minority of 2.6% (4 patients). With regard to possible bias by selection of the sample group, the frequency of posttraumatic movement disorders could be even lower. Movement disorders which occurred in this series are listed in Table 27-2. Postural/ intention tremor phenomenologically similar to enhanced physiological or essential tremor was the most frequent finding. Movement disorders were not disabling and did not require medical therapy in any instance in this series. Patients suffering from “minor” brain injury, that is those with a GCS of 15, developed movement disorders less frequently than those with GCS scores ranging from 9 to 14, the difference being statistically significant.

### General Pathomechanisms in Movement Disorders After Brain Injury

Movement disorders after trauma often have a delayed onset, sometimes up to months or years post-injury. In exceptional cases a delay of more than 20 years has been reported (27). In most patients with movement disorders

**TABLE 27-1**  
*Frequency of Movement Disorders Secondary to Severe Brain Injury*

	TRANSIENT	PERSISTENT
Low frequency intention tremor (2.5 – 4 Hz)	1.4 %	0.9 %
Postural/ kinetic tremor (2.5 – 4 Hz)	–	3.2 %
Postural/ intention tremor (>4 Hz)	4.1 %	3.6 %
Unclassified tremor	4.5 %	1.4 %
Focal dystonia	0.5 %	1.8 %
Hemidystonia	–	0.9 %
Hemidystonia + contralateral focal dystonia	–	0.9 %
Hemidystonia + cervical dystonia	–	0.5 %
Stereotypies	–	0.9 %
Myoclonus	–	0.5 %
Parkinsonism	–	0.9 %
Paroxysmal hypnogenic dyskinesias	–	0.5 %
Hyperekplexia (exaggerated startle)	–	0.5 %

The percentages refer to a cohort of 221 patients (Glasgow Coma Scores between 3 and 8 at the time of trauma) with long-term follow-up at a mean of 3.9 years. Several patients had more than one movement disorder. (from (24) with permission).



**TABLE 27-2**  
**Frequency of Movement Disorders Secondary to Moderate or Mild Brain Injury**

	TRANSIENT	PERSISTENT
Postural/ intention tremor (>4 Hz)	8.2 %	1.3 %
Hyperekplexia (exaggerated startle)	–	0.6 %
Cervical myoclonic twitches	–	0.6 %

The percentages refer to a cohort of 158 patients (Glasgow Coma Scores between 9 and 15 at the time of trauma) with long-term follow-up at a mean of 5.2 years. One patient had both a transient and a persistent movement disorder (from (26) with permission).

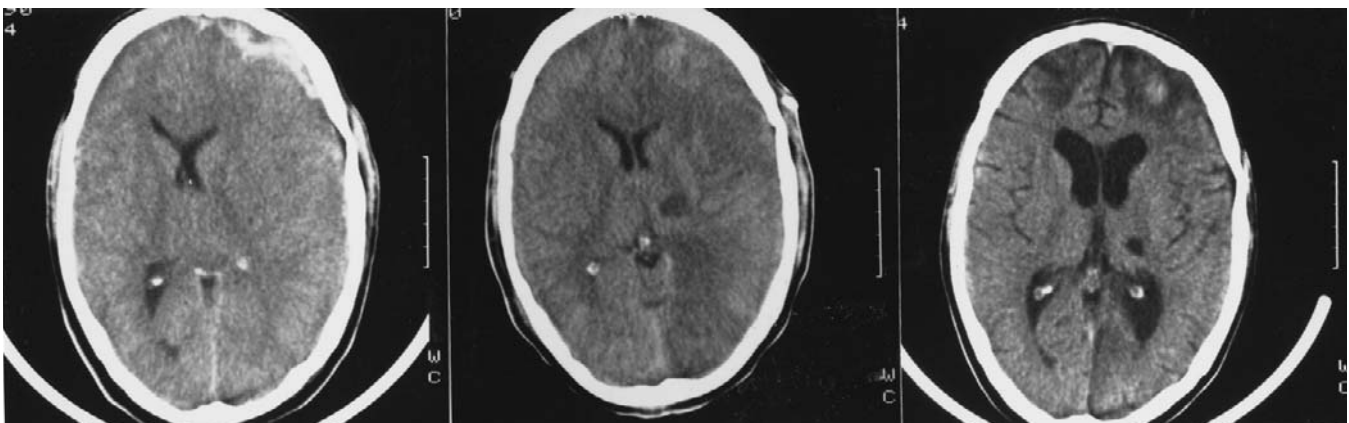
secondary to brain injury structural lesions will be seen with modern imaging techniques. The pathomechanisms resulting in a posttraumatic movement disorder are only partially understood. It is likely that both primary and secondary lesions are responsible for their development. Primary damage involves focal contusions particularly to the basal ganglia and their pathways, DAI with preferential lesions of the superior cerebellar peduncles, and ischemia or hemorrhage due to injury of penetrating arteries associated with rotational forces of the trauma (28, 29). Secondary damage caused by hypoxia, hypotension and increased intracranial pressure may also contribute to the extent of the lesion and the subsequent development of movement disorders. Sequential imaging analyses of the lesions that result in

posttraumatic movement disorders have only rarely been performed (30). Figure 27-1 shows serial CT scans and the development of a thalamic lesion causing focal dystonia. Other factors that might be involved in the pathophysiology of posttraumatic movement disorders include the release of toxic cytokines, other neurotoxins, oxidative stress associated with the deposition of hemosiderin and iron facilitating the production of free radicals and other metabolic effects (31–34). The sequelae of mechanical injury have been studied also at cellular and molecular levels (35, 36). Genetic factors may influence the rate and extent of recovery after severe brain injury (37, 38). The balance between neurodegeneration and restorative neuroplasticity may determine whether a lesion results in permanent damage or in subsequent recovery (39, 40). Restorative processes themselves, however, could also contribute to the development of a posttraumatic movement disorder. Neuroplastic phenomena including aberrant sprouting, ephaptic transmission and alterations of neurotransmitter sensitivity could be responsible for the delay of onset of movement disorders (41).

## DIAGNOSIS OF POSTTRAUMATIC MOVEMENT DISORDERS

### Tremor

The most common posttraumatic movement disorder is tremor. High-amplitude postural and kinetic tremors which may interfere with any motor function are the most disabling tremors (42, 43). Often, the tremor is present



**FIGURE 27-1**

Serial CT scans of a patient who sustained severe head injury at age 23 and suffered from posttraumatic dystonia of his right hand showing the development of a left thalamic lesion thought to be responsible for his focal dystonia. The scan obtained immediately after head injury shows a left frontal subdural hematoma and generalized brain edema (**left**); there is less midline shift 10 days after trauma, but a hypodense lesion in the left thalamus is now visible (**middle**); five weeks later the thalamic lesion is clearly demarcated (**right**). (from (30) with permission)

during the whole range of a movement and increases in amplitude towards reaching the goal. The frequency of these coarse tremors, in general, ranges between 2.5 and 4 Hz and the amplitudes can be larger than 10 cm. The rhythmic oscillatory movements may be interrupted by irregular jerking movements leading to a “myoclonic” appearance (44) and may even resemble “hemiballistic” movements (45). Tremor may be present also at rest. Such slow posttraumatic tremors have been categorized as “mid-brain”, “rubral” or “Holmes” tremors or “myorhythmias” (17, 42, 46, 47). In a series of 35 patients with severe posttraumatic tremor the kinetic component of the tremor was the most prominent feature (48). Bilateral tremor was evident in 10 patients. Commonly, posttraumatic tremor affects predominantly or exclusively the upper extremity. Persistent posttraumatic kinetic tremors are usually secondary to severe closed head injury (48, 49). The most frequent cause is automobile accident with a history of deceleration trauma of the car driver. Kinetic tremors have also been described to occur in pedestrians who were struck by cars and suffered closed head injury. The mean age at trauma was 11 years with a range from 3 to 29 years in one series (48). Most patients are comatose for weeks and often exhibit transient apallic syndromes or akinetic mutism during recovery. The delay between the trauma and the manifestation of the tremor is variable, ranging between 4 weeks up to a year. Commonly, the tremors are associated with ataxia of the affected limb. Tremor almost never is an isolated symptom. Psychological/cognitive alterations were found in 91% of patients, dysarthria in 86%, oculomotor nerve deficits in 69%, truncal ataxia in 91%, and residual hemiparesis or tetraparesis in 91% at a mean of 7 years after brain injury (48).

The history of deceleration trauma and the associated clinical findings indicate that the majority of patients with posttraumatic tremor suffer DAI. This is also supported by neuroradiological findings. In a series of 19 patients with posttraumatic kinetic tremor there was evidence of DAI in 18 patients according to late-phase MR studies revealing corpus callosal atrophy, ventriculomegaly, subcortical lesions and brainstem lesions (50). Lesions of the dentatothalamic pathways were found in 22 out of 25 instances (50). Lesions affecting the predecussational course of the dentatothalamic pathway will result in ipsilateral tremor (Fig. 27-2), while postdecussational lesions are responsible for contralateral tremor (Fig. 27-3). Two of three patients with an accompanying parkinsonian-like rest tremor had lesions involving the substantia nigra (Fig. 27-4). Tremor at rest may be present in patients with lesions of the dentatothalamic pathways without any evidence of contralateral nigrostriatal lesions. Traumatic lesions of the red nucleus and adjacent 3<sup>rd</sup> nerve nucleus may cause ipsilateral ptosis and limitation of ocular adduction and contralateral postural and

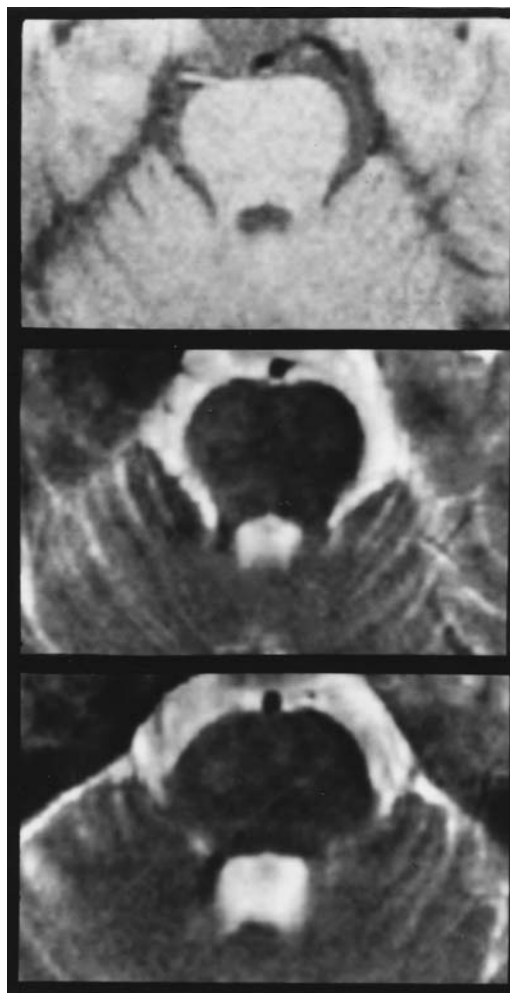


FIGURE 27-2

Axial magnetic resonance imaging studies at 2.0 T in a 27-year-old man with right-sided postural and kinetic tremor 22 years after a traffic accident. T1-weighted images (**upper**) show a small **ipsilateral** hypointense signal alteration of the right brachium conjunctivum adjacent to the fourth ventricle, that is predecussational. Heavily T2-weighted RARE images demonstrate a corresponding apparently larger hypointense lesion (**middle and lower**). (from (50) with permission)

rest tremor (Benedikt’s or Claude’s syndrome) (51). Isolated cases of thalamic lesions have been reported to cause tremor. In both, cerebellar and thalamic tremors the crescendo appearance with goal-directed movements may be the result of amplification of the tremor in reverberating circuits secondary to impaired thalamic relay. The pathophysiologic mechanisms how lesions of the dentatothalamic pathways result in the delayed appearance of tremor have not been fully elucidated (52). It is well known that such lesions trigger both orthograde and retrograde fiber degeneration. Magnetic resonance spectroscopic techniques suggest transsynaptic changes in the development of posttraumatic tremor (53). Transsynaptic

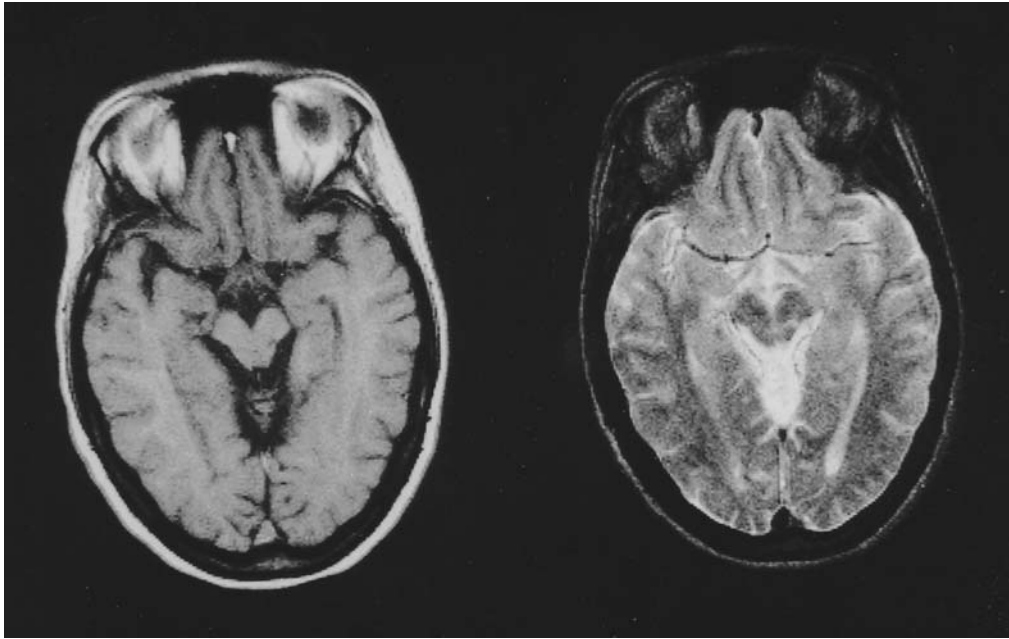


FIGURE 27-3

Magnetic resonance imaging studies at 1.0 T in a 30-year-old woman with right-sided postural and kinetic tremor 12 years after having sustained severe head injury. **The axial scans reveal a small *contralateral* postdecussational lesion not extending to the substantia nigra.** (from (50) with permission)

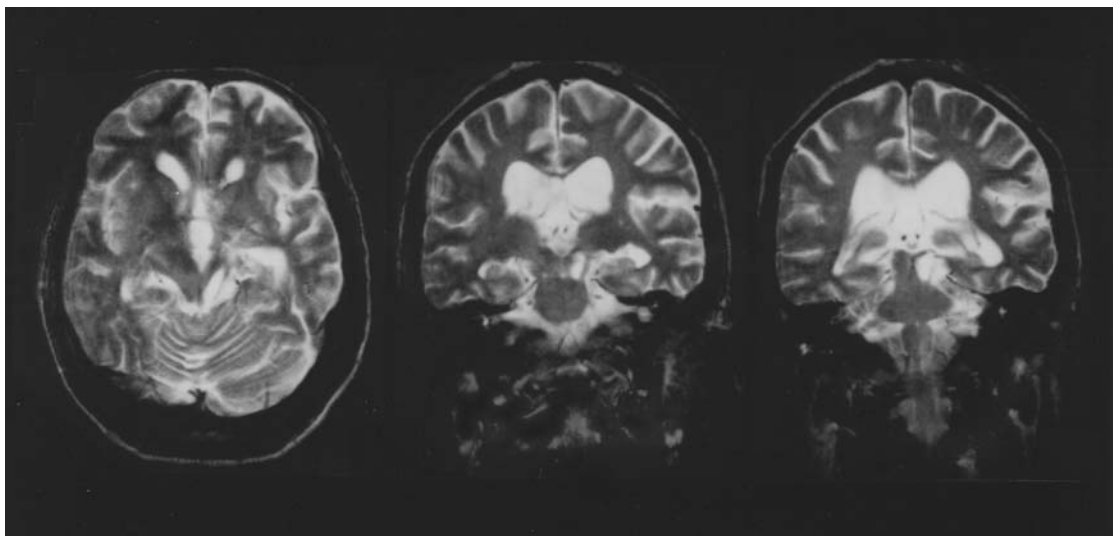


FIGURE 27-4

Magnetic resonance imaging studies at 2.0 T in a 37-year-old man with right-sided parkinsonian tremor at rest, postural and kinetic tremor 33 years after severe head injury. **The axial (left) and coronal (middle and right) scans show a *contralateral* postdecussational lesion extending into the substantia nigra.** (from (50) with permission)

neuronal degeneration could also involve the inferior olives, although palatal myoclonus, a well known symptom in olivary degeneration, is not commonly observed in posttraumatic tremor. Finally, the disinhibition of thalamic

rhythmic network oscillations and modifications of long-loop reflexes could be relevant. Marked decrease in  $^{18}\text{F}$ -dopa uptake in the contralateral striatum without significant changes in the D2-specific binding was found

in patients with posttraumatic ‘midbrain’ tremor who improved with levodopa therapy (54). In another patient with posttraumatic tremor who had a complete contralateral loss of the nigrostriatal pathway after midbrain injury as shown by missing [123]FP-CIT uptake in the contralateral striatum, it was thought that concurrent lesioning of the subthalamic nucleus had prevented the occurrence of parkinsonism (55).

### Dystonia

Hemidystonia is the most typical presentation of post-traumatic dystonia (6, 7, 56–58) (Fig. 27-5). In patient series with symptomatic hemidystonia from different etiologies head injury accounted for 7% to 9% of the cases (59, 60). Rare manifestations of craniocerebral trauma include cervical dystonia, segmental axial dystonia and spasmodic dysphonia (6, 61, 62). The presence of the DYT1 mutation does not seem to increase the risk of secondary dystonia, and the latter is not associated with the DYT1

mutation (63). The DYT1 mutation is found more frequently among dystonic patients with Ashkenazi Jewish origin, and it is characterized by a 3 base-pair deletion in a gene coding for an ATP-binding protein, termed torsinA.

Several patients with posttraumatic hemidystonia were described over the decades since the first report by Austregesilio in 1928 (64). Nevertheless, posttraumatic dystonia is probably underreported. There is a predominance of men which, however, most likely reflects the male preponderance among patients suffering craniocerebral trauma. Age at the time of trauma varies, but almost all patients with only few exceptions were in their infancy or adolescence. It is possible that the delay of onset of dystonia after static brain lesions is associated with the age at trauma. Patients with hemidystonia secondary to brain damage before the age of 7 years had a longer latency between the lesion and the manifestation of dystonia than adults who suffered structural cerebral damage (41). Most patients suffer severe brain injury, but occasional cases of hemidystonia and cervical dystonia were reported after moderate or mild head injury (65). Posttraumatic hemidystonia frequently is preceded by or associated with ipsilateral hemiparesis. The delay between trauma and appearance of hemidystonia is variable and may be as short as one day but may take as long as 6 years (41, 60, 66). In a series of patients with posttraumatic hemidystonia the mean latency between injury and the onset of dystonia was 20 months (6). The natural history of hemidystonia seems to be initial progression with spread over months to years, followed by eventual stabilisation (67).

Posttraumatic dystonia is associated most frequently with basal ganglia or thalamic lesions. Pathoanatomical correlations are similar to those reported for other causes of secondary dystonia (59, 60, 67). Figure 27-6 illustrates typical early magnetic resonance imaging findings in a 19-year-old patient who later developed right hemidystonia. In one series, 7 of 8 patients with posttraumatic hemidystonia had lesions involving the contralateral caudate or putamen (6) (Fig. 27-7). Cases of pallidal lesions resulting in dystonia are rare (68, 69) (Fig. 27-8). Occasionally, hemidystonia or focal dystonia, in particular, hand dystonia, is associated with thalamic lesions (30). A contralateral mesencephalic lesion was found in a patient with hemidystonia plus torticollis (6) (Fig. 27-9). Patients with posttraumatic kinetic tremor due to mesencephalic lesions or to lesions of the superior cerebellar peduncles may also have mild dystonic postures (48).

Primary as well as secondary factors are likely to contribute to the basal ganglia lesions in posttraumatic dystonia. Some of the caudatoputamenal lesions in posttraumatic hemidystonia correspond to vascular territories, in particular to the anterior (and more rarely posterior) group of the lateral lenticulostriate branches of the middle cerebral artery. Stretch of these vessels by rotating forces may either result in hemorrhage or in ischemia secondary to lesions of



FIGURE 27-5

Clinical presentation of patients with posttraumatic dystonia. **A:** patient with right-sided hemidystonia and cervical dystonia, before thalamotomy. **B:** same patient at long-term follow-up after left-sided thalamotomy. **C:** dystonic posture of right hand. **D:** left-sided dystonia with superimposed athetotic movements. **E:** right-sided hemidystonia. **F:** typical increase of dystonia upon intended movement. (from (6) with permission)

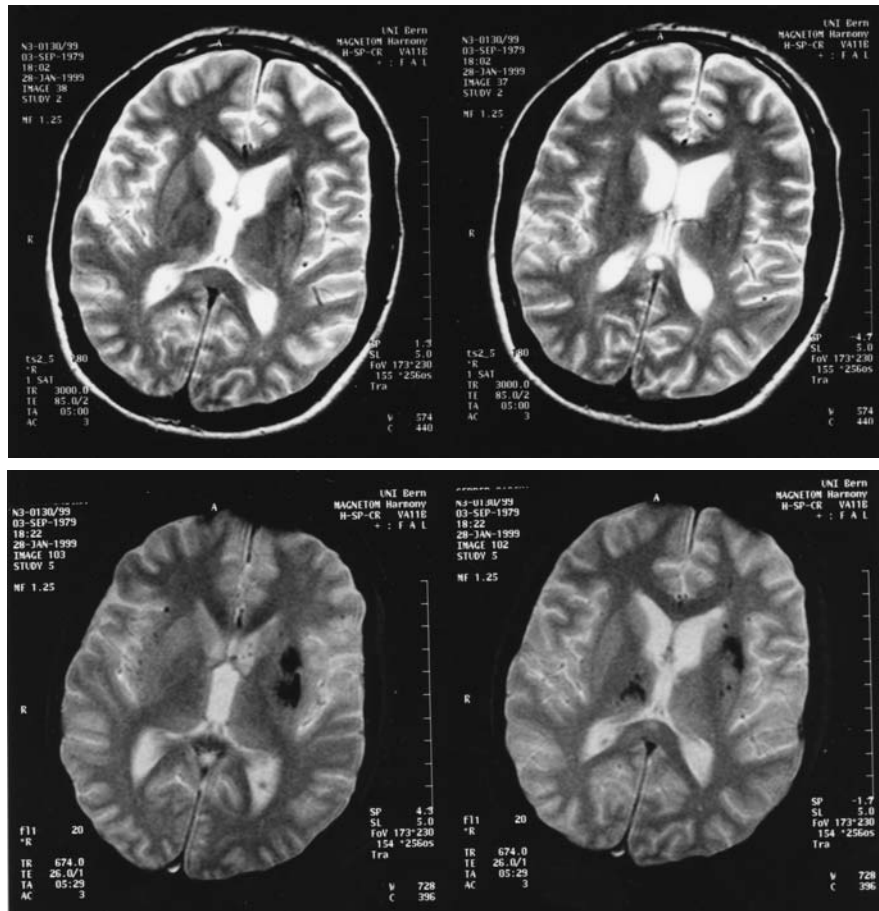


FIGURE 27-6

Magnetic resonance imaging studies of a 19-year-old man two months after suffering severe closed head injury with an initial Glasgow Coma Score of 4. Later on, right hemidystonia and cervical dystonia developed. **Upper row:** Axial Turbospin-Echo 3000/85 scans show poorly defined lesions of the left putamen. **Lower row:** Axial T2 FLASH 674/26 sequences which are more susceptible to hemosiderin better demonstrate the extent of the hypointense lesions in the putamen and reveal other small lesions in addition. (from (14) with permission)

the intima (70). This mechanism is probably also responsible for the fact that in patients with dystonia due to brain injury as compared to patients with other secondary dystonia, caudotoputaminal lesions are much more frequent than thalamic lesions (59). In general, the prognosis of traumatic basal ganglia hematoma is poor. In a recent series, only 6 of 34 patients (16%) made a favorable recovery (28). Rarely, blunt or penetrating carotid artery injuries have been described to result in ischemic cerebral lesions with subsequent development of dystonia (71, 72). Secondary damage to the basal ganglia is also possible. Many patients with posttraumatic dystonia were reported to have hematoma contralateral to the hemidystonia as well. Hypoxia is known to result in damage following “topistic” patterns, i.e. damage of specific nuclei or to neuronal subpopulations such as selective striatal vulnerability, for example (73).

Deranged function of both the direct and the indirect striatopallidal pathways is thought to underly the

development of dystonia. Regional cerebral blood flow studies in acquired hemidystonia secondary to basal ganglia or thalamic lesions have shown frontal overactivity on movement indicating that dystonia ultimately is due to thalamofrontal disinhibition secondary to disruption of the normal inhibitory control by the basal ganglia (74). It is puzzling that isolated lesions of the globus pallidus internus in healthy people can result in dystonia, but lesioning or stimulation of the same structure in dystonic people can alleviate dystonia. This observation, nevertheless, emphasizes that disturbed pallidal discharge and subsequent deranged pallidothalamic output is responsible for secondary dystonia (75).

### Ballism and Chorea

Overall, ballism is a rare movement disorder. There have been occasional descriptions of hemiballism and hemichorea

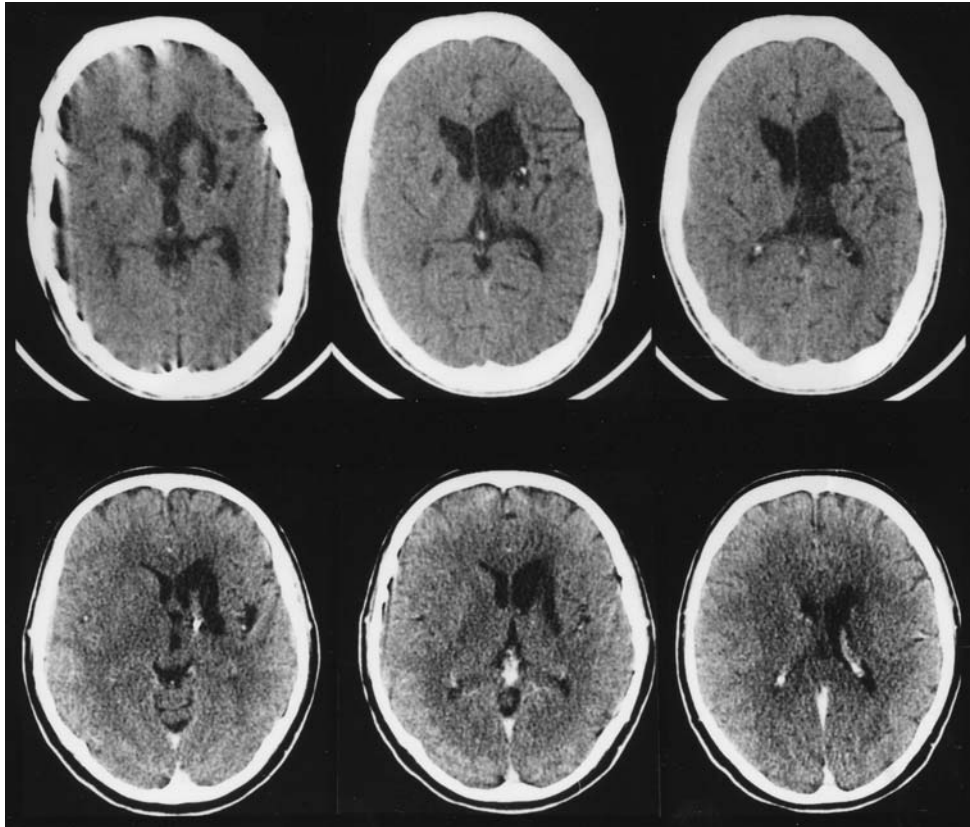


FIGURE 27-7

CT scans of a 21-year old man who sustained a severe closed head injury at age 7 and subsequently developed *bilateral* hemidystonia. On the left side there is a lesion of the caudate, anterior internal capsule and putamen corresponding to supply of lateral lenticulostriate branches of middle cerebral artery and small lesions of the ventrolateral thalamus; on the right side there is a lesion of anterior putamen (**upper**). CT scans showing a caudatoputaminical lesion in a 50-year old woman who sustained a moderate brain injury at age 9 and who developed contralateral hemidystonia 4 years thereafter (**lower**). (from (6) with permission)

secondary to craniocerebral trauma (19, 68, 76, 77). While some reports appear to describe true hemiballism, the categorization of the movement disorder remains somewhat unclear in other instances (45, 78). Often, the term “violent” movement disorder has been wrongly used to assign the diagnosis of hemiballism in patients with large amplitude hyperkinesia including tremors with superimposed irregular myoclonic jerks. Posttraumatic hemiballism is associated with severe closed head injury. It may occur with a delay of weeks or months when patients recover from coma. Histopathological examination revealed subthalamic nucleus atrophy in a patient with a traumatic pallidal lesion who developed hemiballism at 2 years postinjury (68). In another patient with posttraumatic hemiballism, no structural abnormalities were found with conventional imaging studies but single photon emission computed tomography (SPECT) revealed a subthalamic lesion (79).

Choreatic movement disorders may be caused by epidural or subdural hematomas in the rare case (80). Chronic subdural hematomas may present with contralateral, ipsilateral or bilateral choreatic movements (81, 82).

### Paroxysmal Dyskinesias

The pathophysiology of paroxysmal dyskinesias remains unclear. It has been assumed that they present a certain type of subcortical epilepsy or reflex epilepsy. They are also thought to be associated with dysfunction of sensory processing at the level of the basal ganglia or the thalamus. There have been several reports on paroxysmal dyskinesias secondary to brain injury (83–90). Imaging findings have been inconclusive. In single cases putaminal lesions were found (83). Positron emission tomographic scan studies showed abnormal metabolism in the

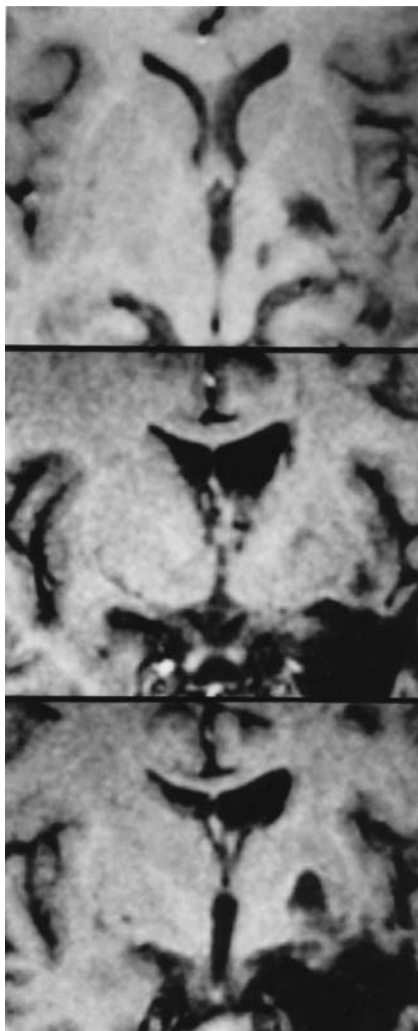


FIGURE 27-8

Magnetic resonance imaging studies in a 32-year-old man with posttraumatic hemidystonia after severe head injury at age 7. The axial scan through the lower part of basal ganglia (**upper**) shows the posttraumatic pallidal lesion extending to posterior putamen and a small lesion in the subthalamic region after stereotactic surgery which provided partial relief of the hemidystonia for more than 16 years. The coronal scans (**middle and lower**) more clearly show the additional lesion to the putamen. (from (6) with permission)

contralateral basal ganglia during an attack of paroxysmal posttraumatic hemidystonia (87).

### Tics and Tourettism

Adult-onset disorders with both motor tics and vocalizations secondary to a known cause have been referred to as “tourettism” to contrast it with the more common idiopathic Tourette’s syndrome (91). Posttraumatic tics and tourettism following head trauma have been described in few patients (92–96). Since tics are relatively common, the coincidental occurrence of tics after head trauma must

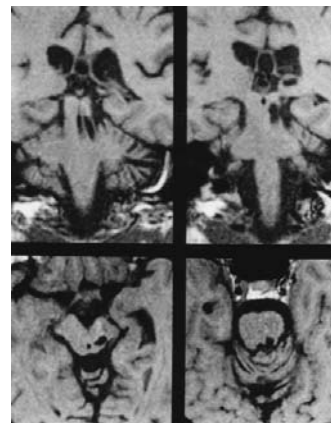


FIGURE 27-9

Magnetic resonance scans of a 28-year-old man with right-sided hemidystonia and cervical dystonia. The coronal images show a longish pontomesencephalic tegmental lesion on the left side (**upper row**). The axial scans demonstrate more clearly the lesion also affecting the dentatothalamic pathway thought to be responsible for the additional tremor in this case (**lower row**). (from (6) with permission)

always deserve special consideration. A causative role of trauma is favored in patients with evidence of other posttraumatic sequelae, and a negative history of motor tics prior to head injury. A history of well documented trauma to the head is mandatory. The older age at onset of patients with posttraumatic tourettism is notable, in contrast to Tourette’s syndrome. We studied the characteristics in 6 patients with tics secondary to craniocerebral trauma (93). All patients were male and the mean age at the time of the trauma was 28 years. Craniocerebral injury was moderate or mild in 5 patients, and neuroimaging studies did not reveal basal ganglia lesions. In another patient who had tics and marked obsessive-compulsive behavior secondary to severe brain injury, extensive periventricular and subcortical leukoencephalopathy was detected by magnetic resonance imaging studies (93) (Fig. 27-10). Preexisting tics may exacerbate after head injury (13). Secondary, including posttraumatic tic disorders were recently reviewed (97).

### Other Posttraumatic Hyperkinesias

Various other hyperkinetic movement disorders, often in the frame of case reports, were reported after craniocerebral trauma including instances of myoclonus, opsoclonus, palatal myoclonus, stereotypies, akathisia, and galloping tongue (98–105).

### Posttraumatic Parkinsonism and Parkinson’s Disease

*Parkinsonism after Single Head Injury* Although the concept of posttraumatic parkinsonism was well accepted in

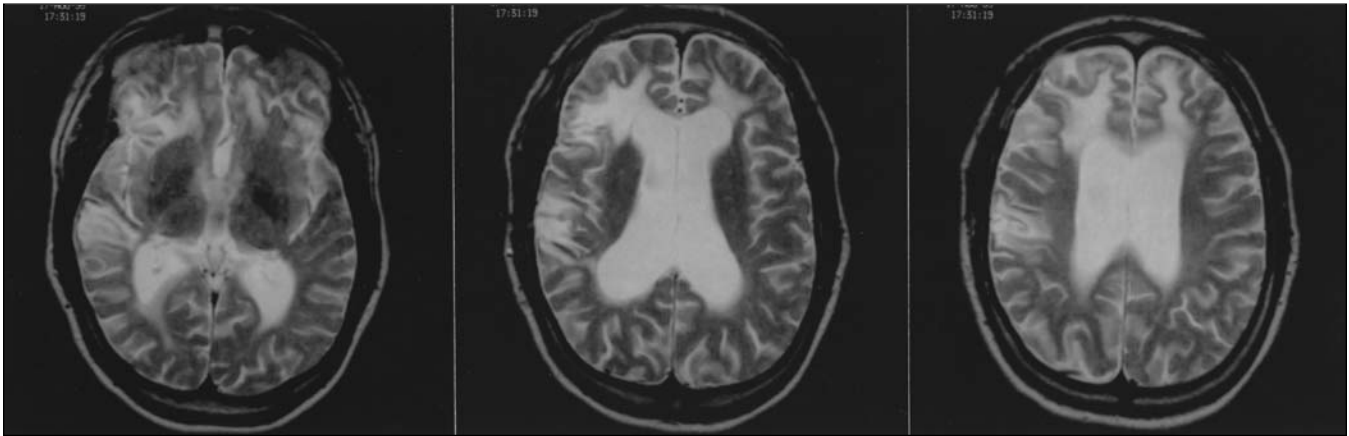


FIGURE 27-10

Magnetic resonance imaging studies of a 33-year-old man with posttraumatic tics and obsessive-compulsive behavior 12 years after he sustained a series of two severe head injuries. There is panventricular dilatation, cortical atrophy, and extensive periventricular and subcortical leukoencephalopathy, particularly of the frontal and the right temporoparietal white matter. There are no focal basal ganglia lesions. (from (91) with permission)

the first part of the 20th century, review of cases in the literature raises doubts that most are truly examples of parkinsonism resulting from trauma (106, 107). The causal relationship in most cases has been largely speculative and the interpretation complicated by medicolegal issues. In some cases, the initial injury actually seemed to have resulted from, rather than caused, motor impairment. Posttraumatic parkinsonism, in general, is secondary to severe closed head injury (108, 109). Occasionally, parkinsonism has been described to be associated with lesions of the substantia nigra (110, 111). Direct lesions to the substantia nigra have been reported secondary to injuries by knives, screwdrivers, shell splinters or gunshots, and usually present with hemiparkinsonism (112–114). The parkinsonian syndrome is dominated by akinetic-rigid symptoms. Other movement disorders and pyramidal dysfunction may be present. We have recently studied a young man who suffered acute flexion-extension injury playing American football, followed by 3-week coma attributed to bilateral hemisphere hemorrhage, who is left with residual, levodopa-responsive parkinsonism, without any evidence of damage to the substantia nigra on imaging studies.

There have been several reports of parkinsonism secondary to chronic subdural hematoma (115). Parkinsonian symptoms become evident within weeks after trivial head injury. The clinical picture is dominated by hypomimia, bradykinesia and tremor. Other neurological signs and symptoms are usually present, although some instances of pure parkinsonism have been described (115, 116). Diagnostic evaluations appear to be delayed and initial misinterpretations are common. Favorable outcome is achieved in most instances after drainage of

the hematoma with complete or almost complete remission of parkinsonism. Chronic subdural hematomas may also cause deterioration of preexisting parkinsonian syndromes (115). Also, acute subdural hematomas when associated with brainstem compression and reduced fluorodopa uptake in the contralateral putamen can induce a hemiparkinsonian syndrome (117).

*Parkinsonism after Repeated Head Injury* Boxing is the most frequent cause for parkinsonism associated with repeated head trauma (118–122). Obvious tremors, bradykinesia and hypophonia in Muhammed Ali has helped to draw the public attention to this problem. Although cumulative brain injury occurs also in other professional sports (123), only exceptional instances of parkinsonism have been reported (122). “Pugilistic” parkinsonism (PP) or “punch-drunk” syndrome is a chronic encephalopathy which results from the cumulative effects of subclinical concussions secondary to rotational acceleration traumas by direct blows to the head. Usually, PP appears with a delay of several years after ending an active boxing career (124). The frequency of PP has been estimated to range between 20% to 50% of professional boxers. The severity of PP correlates with the length of the boxing career and the number of bouts (125). Clinically, a variable spectrum of signs and symptoms can be present including behavioral changes, dementia, and corticospinal and cerebellar symptoms. Another frequent finding is marked dysarthria or hypophonia. In contrast to posttraumatic parkinsonism secondary to a single severe head injury, tremor at rest is a relatively frequent feature of PP. In addition to extensive nigral damage, dysfunction of striatal dopaminergic terminals



has been suggested. Proton magnetic resonance spectroscopy studies have demonstrated a significant reduction in the concentration of N-acetylaspartate in the lenticular nuclei of PP patients as compared to controls and PD patients (126). PET studies showed uniform nigrostriatal involvement but relative sparing of caudate function in PP (122). Neuropathological studies have revealed depigmentation of the substantia nigra but an absence of Lewy bodies, the histological hallmark for PD. While the number of fatalities has decreased steadily over the years due to preventive measures in the ring it remains to be seen whether this will result also in a decrease of PP among boxers (127). There has been controversy as to the development of chronic encephalopathy in amateur boxing. Most studies do not show clinical evidence of chronic encephalopathy (128). In one study finger-tapping performance was worse in some amateur boxers as compared to other athletes (129). It has been shown recently that high-exposure professional boxers with an apolipoprotein epsilon4 allele have significantly greater scores on a scale measuring chronic encephalopathy than those without the allele (130). Thus, genetic susceptibility to the effects of repeated head trauma is likely.

*Parkinson's Disease and Head Trauma* In his original *Essay on the Shaking Palsy* James Parkinson suggested that the disease that now bears his name might result from trauma to the medulla. Head trauma as a possible risk factor for PD has been the subject of controversy for years (8, 9, 131–134). It has been shown that head trauma sustained in motor vehicle accidents can exacerbate parkinsonism transiently in patients with PD, however, without resulting in increased persistent disability or acceleration of the clinical course of the disease (135). Several studies have found a higher frequency of head injury in patients with PD (136, 137). Usually, the history of head trauma dates back to 20 or 30 years prior to onset of PD and, therefore, any cause-and-effect relationship is difficult to establish. With regard to head injury and other possible environmental factors it has been suggested that PD might be the consequence of clinically silent exposure in early or middle life with symptoms becoming manifest only later when there is a further decline of dopaminergic neurons with advancing age. Some studies suggested that susceptibility to trauma is more important than the severity of trauma itself. Several studies which have shown a positive association between head injury and trauma suffer from methodological flaws. The major problem with retrospective case control studies is recall bias. Unfortunately, there is a paucity of cohort studies which might be better suited to answer the inherent questions. One cohort study did not detect a significant increase in standardized morbidity ratios for PD in adults with head injury (138).

However, this study had a 30% probability of not detecting a hypothetical twofold relative risk. In a recent case-control study, subjects who experienced a mild head trauma with only amnesia had no increased risk for PD; however, subjects who had a mild head trauma with loss of consciousness or a more severe trauma had a much higher odds ratio (9). Since head trauma, overall, was considered rather a relatively rare event, the population attributable risk was estimated to be at 5%.

## TREATMENT OF POSTTRAUMATIC MOVEMENT DISORDERS

Rehabilitation of patients with posttraumatic movement disorders must consider both associated neurological and psychosocial dysfunction resulting from brain injury and the specific movement disorders. The physical disability of patients with severe kinetic tremors can be extreme because they are neither able to reach or to manage an object when the syndrome is fully expressed. Their disabilities should be treated according to the standard principles of rehabilitation care. It is important to anticipate and prevent potential obstacles for reintegration, to identify and offer strategies to manage present disabilities, and to develop adaptive and coping skills to achieve more independence. Physical therapy is helpful to prevent contractures in the most severely affected cases with dystonia.

### Tremor after Severe Brain Injury

*Medical Treatment* It is difficult to predict the prognosis of posttraumatic tremor in the initial period after its manifestation. It may lessen or resolve spontaneously within 1 year after its onset. The majority of patients, however, have persistent violent shaking movements. Posttraumatic tremor, then, is notoriously difficult to treat. Only few patients have been reported to respond favorably to medical treatment. Drugs reported to improve posttraumatic tremor include glutethimide, isoniazid, L-tryptophan, propranolol, benzodiazepines, carbamazepine, levodopa/carbidopa and anticholinergics (53, 139–141). Botulinum toxin injections may be helpful to relief the tremor temporarily but the high dosages administered to both proximal and distal arm muscles limit the usefulness of this treatment (142).

*Surgical Treatment* The largest surgical experience for posttraumatic tremor comes from ablative functional stereotactic surgery with radiofrequency lesioning in the ventrolateral thalamus and the subthalamic region, which can effectively abate posttraumatic tremor (45, 48, 143–160) (Fig. 27-11). The data of a total of 128 patients who underwent ablative stereotactic surgery as documented in

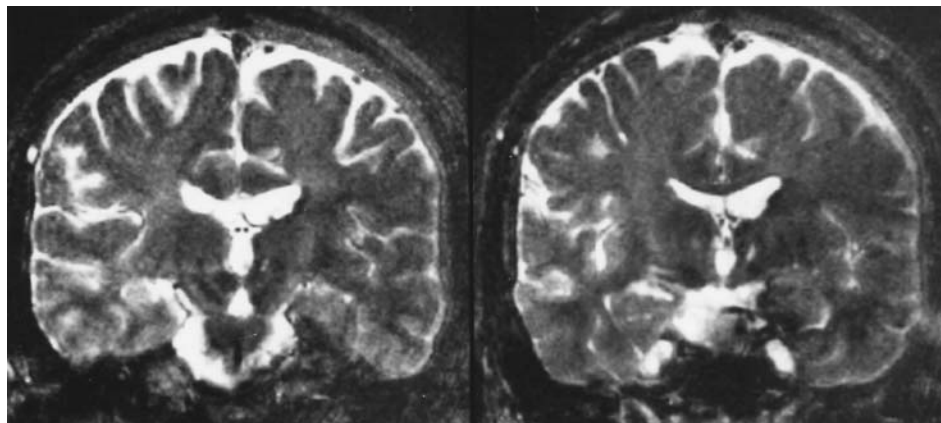


FIGURE 27-11

Magnetic resonance imaging studies obtained 3 years after combined ablative stereotactic surgery in the ventrolateral thalamus and zona incerta for treatment of posttraumatic tremor of the right arm. The coronal scans demonstrate the location of the small left stereotactic lesion and its topography in relation to adjacent nuclei. (from (48) with permission)

the literature are shown in Table 27-3. Persistent improvement on long-term follow-up has been observed in 88% of patients with the tremor being absent or markedly reduced in 65% in one study (48). Tremor at rest usually is completely abolished but the most striking improvement is the reduction of postural and kinetic tremor. Also, valuable gain in functional disability has been achieved. Functional improvement was more striking in patients who had severe incapacitating tremor but comparatively less other neurological or mental deficits. There is a marked risk for adverse effects, however, in this vulnerable group of patients. Immediate postoperative side effects have been reported to occur in 50% to 90% of patients and persistent side effects are being observed in up to 63%. Most frequently, such side effects consist chiefly of aggravation of preoperative symptoms such as dysarthria or gait disturbance. There is a trend for patients with left-sided surgery to present more frequently with increased dysarthria than patients who have right-sided procedures. Surprisingly, single patients may benefit from marked amelioration of their dysarthria after radiofrequency lesioning (48). On long-term follow-up, it has been observed that there may be an increase in dystonic postures despite improvement of tremor, or new dystonic symptoms may become manifest. It is unclear whether this is related to the surgical procedure or whether this may present delayed-onset dystonia (41). The high frequency of side effects is remarkably different from that observed after thalamotomy for other types of tremor, for example, essential tremor. The size of the lesions necessary to control severe kinetic tremors has been debated. It has been stated that larger lesions should be made in such cases to achieve long-term relief (154). On the other hand, with regard to the propensity of these patients for postoperative

morbidity, small lesions in the basal ventrolateral thalamus and the subthalamic region involving the zona incerta might be more advantageous. Gamma knife Vim thalamotomy has been reported also to result in modest improvement in posttraumatic tremor (161), but delayed effects of radiation may limit this procedure.

There is relatively little experience with thalamic deep brain stimulation (DBS) for treatment of posttraumatic tremor (162–167). Similar to other kinetic tremors due to stroke or multiple sclerosis (168), DBS has been found to be less effective than in parkinsonian tremor or essential tremor (Table 27-4). Occasionally, thalamic DBS was described as completely ineffective (166). In other instances, however, patients achieved variable symptomatic and functional benefit. It appears that DBS may be less effective in control of tremor but is associated with less side effects than radiofrequency lesioning in this special group of patients. Long-term follow-up data is very limited. There have been divergent opinions what should be considered the ideal thalamic target for DBS to treat proximal kinetic tremors. Nguyen et al. suggested that proximal contacts in the Vim would be most beneficial (165), whereas others think that stimulation of a target located more anteriorly is important (167). Kitagawa et al. recently demonstrated that stimulation of the subthalamic area can be effective in patients with proximal tremors (169). Electrodes placed in the zona incerta were most effective to control contralateral tremor. We recommend to wait at least one year after onset of posttraumatic tremor before surgery is considered. Further studies are clearly necessary to establish the role of DBS in posttraumatic tremor. We prefer DBS over thalamotomy in these patients regarding the high occurrence of side effects, presently.

**TABLE 27-3**  
**Functional Stereotactic Surgery for Posttraumatic Tremor: Lesioning Procedures**

AUTHOR(S) AND YEAR	TARGET	CASES	IMMEDIATE IMPROVEMENT	LONG-TERM FOLLOW-UP	LAST FOLLOW-UP, MEAN YRS (RANGE)	SYMPTOMATIC IMPROVEMENT (%)	FUNCTIONAL IMPROVEMENT (%)	PERSISTENT SIDE EFFECTS
Cooper, 1960	VL	2	2	1	1.3	1/1	1/1	NA
Spiegel et al., 1963	STR	1	1	1	NA	0/1	NA	NA
Fox and Kurtzke, 1966	VL	1	1	1	0.5	1/1	1/1	0/1
Samra et al., 1970	VL	5	5	NA	NA	5/5 (100)	NA	NA
Van Manen, 1974*	VL	2	2	2	7	1/2	NA	1/2
Eiras and García, 1980	GP, Vop	1	1	1	2.5	1/1	1/1	0/1
Andrew et al., 1982	VL	8	8	NA	NA	8/8 (100)	8/8 (100)	5/8 (63)
Kandel, 1982*	VL, STR, GP	10	NA	NA	NA	NA	NA	NA
Niizuma et al., 1982*	Vim, Sub-Vim	3	3	NA	NA	NA	NA	NA
Ohye et al., 1982	Vim	8	8	NA	NA	NA	NA	1/8 (13)
Hirai et al., 1983	VL	5	4	NA	NA	NA	NA	0/5
Bullard and Nashold, 1984	VL	7	7	7	1.5 (0.2 to 3)	7/7 (100)	6/7 (86)	3/7 (43)
Bullard and Nashold, 1988**	VL	10	10	8	1.3 (0.2 to 3)	8/8 (100)	7/8 (90)	4/8 (50)
Iwadata et al., 1989	VL	3	2	NA	NA	2/3 (66)	NA	NA
Richardson, 1989	VL	1	1	NA	NA	1/1	NA	NA
Goldman and Kelly, 1992	VL	4	4	4	3 (1.4 to 4.5)	3/4 (75)	3/4 (75)	0/4 (0)
Marks, 1993	Vim	7	6	NA	NA	6/7 (86)	NA	1/7 (14)
Taira et al., 1993	Vop, Vim	3	1		3		0.5	1/3 (33)
NA	2/3 (66)							
Krauss et al., 1994	VL, Zi	35	35	32	10.5 (0.5 to 24)	28/32 (88)	26/29 (90)	12/32 (38)
Jankovic et al., 1995	Vim	6	6	6	4	6/6 (100)	3/6 (50)	3/6 (50)
Shahzadi et al., 1995*	Vim	11	11	NA	NA	NA	NA	6/11 (55)
Louis et al., 1996	VL	2	2	2	0.3 and 4	2/2	NA	NA
Total		128	113/118 (96%)	68 (53 %)		81/92 (88 %)	56/65 (86 %)	38/103(37%)

*Target:* GP = globus pallidus; STR = subthalamic region; Vim = (nucleus) ventralis intermedius (thalami); VL = ventrolateral thalamus; Vop = (nucleus) ventrooralis posterior (thalami); Zi = zona incerta.

NA = not available.

\* Series with tremors of different etiologies, usually cerebellar-type tremors. Specific data for posttraumatic tremor not always available.

\*\* The series of Bullard & Nashold from 1988 includes the patients in the series from 1984. (from (14) with permission).

**TABLE 27-4**  
**Functional Stereotactic Surgery for Posttraumatic Tremor: Deep Brain Stimulation**

AUTHOR(S) AND YEAR	TARGET	CASES	IMMEDIATE IMPROVEMENT	LONG-TERM FOLLOW-UP	LAST FOLLOW-UP, YEARS	SYMPTOMATIC IMPROVEMENT	FUNCTIONAL IMPROVEMENT	PERSISTENT SIDE EFFECTS
Andy, 1983	CM-PF, Zi	1	1	NA	NA	1/1	1/1	0/1
Broggi et al., 1993	Vim	1	1	1	0.8	1/1	1/1	0/1
Nguyen and Degos, 1993	Vim	1	1	1	1	1/1	1/1	0/1
Benabid et al., 1996*	Vim	X/7	NA	NA	NA	“inconsistently, less significantly, or not improved”	“significant improvement observed in the quality of daily living”	NA
Standhart et al., 1998	Vim	1	0	NA	NA	0/1	NA	NA
Nobbe, 2000**	Vop	1	1	1	0.5	1/1	1/1	0/1
Krauss, 2000**	Vop/Vim	1	1	1	1.5	1/1	1/1	0/1
Vesper et al., 2000	Vop/Vim	4	4	4	0.5	4/4	4/4	NA

*Target:* CM-PF = centrum medianum – (nucleus) parafascicularis (thalami); Zi = zona incerta.

NA = not available.

\* Series with tremors of different etiologies, usually cerebellar-type tremors. Specific data for posttraumatic tremor not always available.

\*\*Unpublished data.

(from (14) with permission).

### Tremor After Moderate and Mild Brain Injury

The postural and intention tremors that may occur after mild and moderate head injury usually do not require therapy and subside spontaneously (26). In some patients tremor persists and head tremor can also develop. In those cases medical therapy with clonazepam, propranolol or primidone, or botulinum toxin injections may provide relief (170, 171).

### Dystonia

*Medical Treatment* In patients with posttraumatic dystonia, spontaneous remission is unusual, although some improvement can be seen particularly in patients with thalamic lesions. Medical treatment is usually ineffective. Occasionally, there is a mild response to anticholinergic drugs. Botulinum toxin injections are the treatment of first choice in patients with posttraumatic torticollis and other focal dystonias (18, 142).

*Surgical Treatment* The prognosis is favorable in the rare cases of dystonia related to subdural hematoma after drainage of the hematoma (172–174). Functional stereotactic surgery is a treatment option in patients with disabling hemidystonia or segmental dystonia (6, 175). Targets include ventrolateral thalamus, the subthalamic region, the pulvinar and the globus pallidus internus. Improvement of dystonia in the early postoperative period has been described in most instances. Experience with long-term follow-up, however, is limited (Fig. 27-9). At a mean follow-up of 18 years after thalamic radiofrequency lesioning, 3 of 6 patients with posttraumatic hemidystonia still benefited from some improvement of their hemidystonia (6). Recently, pallidal surgery has been reintroduced for treatment of dystonia (176). In contrast to thalamotomy, the improvement after pallidotomy may be delayed by several weeks or months. It is unclear at this time whether thalamic or pallidal targets should be preferred in patients with secondary dystonia (177). In a series of patients with various forms of dystonia, the response to pallidal surgery for dystonia was dependent on etiology (178). Patients with secondary dystonia who had extensive structural cerebral lesions had no improvement after pallidal surgery, whereas patients with primary dystonia, particularly those with DYT1 dystonia, had striking benefit and patients with secondary dystonia without structural lesions had mild benefit. Villemure and colleagues reported on two dystonia patients with secondary dystonia who did not improve with pallidal surgery but benefited with thalamic targets (179). In a recent study, on the other hand, no difference in outcome between pallidal or thalamic targets was seen in patients with secondary dystonia (180). Overall, patients with secondary dystonia experienced more modest improvement

as compared to patients with primary dystonia regardless of the target used. The response of posttraumatic dystonia to pallidotomy appears to be difficult to predict. We did not observe improvement of posttraumatic hemidystonia after pallidotomy in a young patient despite his imaging studies did not show structural brain lesions. In contrast, bilateral pallidotomy was reported to result in marked improvement in a patient with generalized posttraumatic dystonia (181).

DBS has been used in only few patients with hemidystonia secondary to craniocerebral trauma. Marked improvement of dystonic movements and postures has been described in a 16-year-old boy with a thalamic lesion who underwent stimulation of the ventroposterolateral thalamus over 8 months (182). We have followed a patient for 6 years who continues to show consistent improvement of posttraumatic dystonia of the left arm with stimulation of the contralateral globus pallidus internus (183) (Fig. 27-12). Chronic intrathecal baclofen administered via implanted pumps may provide useful improvement in patients with more generalized dystonia or accompanying spasticity (184–186).

### Ballism and Chorea

In contrast to vascular hemiballism, posttraumatic hemiballism seems to be more persistent with less tendency for spontaneous improvement. Patients who do not respond adequately to conservative treatment, such as tetrabenazine, a monoamine depleting drug, can benefit from functional stereotactic surgery (187). Due to the rarity of posttraumatic hemiballism, however, experience is very limited. Targets in the contralateral pallidum or thalamus are useful.

In chorea associated with chronic subdural hematoma, the prognosis usually is favorable after drainage of the hematoma.

### Paroxysmal Dyskinesias

Posttraumatic paroxysmal dyskinesias often respond favorably to anticonvulsive medication, in particular kinesigenic dyskinesias (90). Thalamic stimulation has been shown to be beneficial in a patient with paroxysmal non-kinesigenic dyskinesia (188).

### Posttraumatic Parkinsonism

Patients with substantia nigra lesions may benefit from levodopa therapy (111). Medical treatment of posttraumatic parkinsonism, in general, is similar to that for idiopathic PD (189). There are no data available for the specific outcome of functional stereotactic surgery in patients with parkinsonism secondary to brain injury.



FIGURE 27-12

**A:** Stereotactic T2-weighted axial magnetic resonance scan of a 24-year-old man who sustained severe closed head injury at age 15 and who subsequently developed left-sided low-frequency tremor and hemidystonia. The tremor was successfully relieved by a right-sided thalamotomy; hemidystonia, however, increased over the years. This MR image was used for target calculation to implant an electrode in the posteroventral lateral globus pallidus internus (sides are reversed). **B:** Axial CT scan 4 years later demonstrating the position of the electrode in the pallidal target providing relief of dystonic posture and phasic movements and dystonia-associated pain. (from (180) with permission)

## CONCLUSIONS

Traumatic brain injury can result in a variety of movement disorders. The mediation of the effects of trauma and the pathophysiology of the development of post-traumatic movement disorders require further study.

Proper identification of such movement disorders is pivotal for rehabilitation. Functional stereotactic neurosurgery should be considered in patients with disabling movement disorders refractory to medical treatment.

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# 28

## Balance and Dizziness

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### INTRODUCTION AND OVERVIEW

While a large number of different etiologies can be the cause for complaints of dizziness (representing a wide variety of specific symptoms) and imbalance, traumatic brain injury (TBI) ranks among those of significant complexity and difficult to rehabilitate. Patients diagnosed with TBI often present with dizziness complaints in the midst of a wide variety of other symptoms, as is evidenced by the diversity of discussion in this text. Experience in treating this group of patients for imbalance and other dizziness complaints shows that the time course of recovery is significantly longer than patients with similar damage to the peripheral or central balance system, yet for reasons other than TBI. To date, as a group those with TBI diagnoses do poorer overall in treatment formats of Vestibular and Balance rehabilitation therapy than other groups with peripheral vestibular injuries, not of a head injury origin. The assumption used to explain these differences in time and level of recovery during group comparisons, is that there are co-morbidities of a central nervous system origin, not distinguished by traditional diagnostics that cause the interference with recovery. Additionally, there are known disorders that can develop secondary to a TBI that are known to limit and slow down recovery of balance and dizziness complaints such as post-traumatic stress syndrome and other psychiatric conditions, or development

of post-traumatic migraine or seizure disorders, all discussed elsewhere in this text.

The purpose of this chapter is to provide an introductory review of the potential sources of complaints of vertigo, lightheadedness and imbalance that can result from a traumatic brain injury. Additionally, the chapter will review the various direct treatment options for these resulting conditions, the principle one being that of Vestibular and Balance Rehabilitation Therapy (VBRT).

For reference it will be useful to start with a brief overview of the elements of the balance system and its normal functioning.

No single structure subserves balance function. Rather, the system consists of multiple sensory inputs from the vestibular end organs, the visual system, and the somatosensory/proprioceptive systems. The input information is then integrated at the level of the brain stem and cerebellum with significant influence from the cerebral cortex, including the frontal, parietal, and occipital lobes. The integrated input information results in various stereotypic responses for eye movement, postural control, and perception of movement and orientation in space. Only a brief overview of the major elements of the input and output structures and their basic physiological functioning will be provided here, other literature providing detailed descriptions is available (1–5).

When considering the function of the balance system, it is helpful to view it in light of the major functional

purposes that the system attempts to accomplish. One can view these purposes as three distinct areas:

- Perceptions of orientation relative to gravity, the direction and speed of movement and when a change in the attitude of movement occurs.
- Maintenance of clear visual imaging of the seen world with the head in motion, target in motion or both in relative motion.
- Ability to maintain static and dynamic upright stance, and to perform volitional movements ranging from routine ambulation to complicated sequences involved in sports, dance etc. There are two areas that sub serve this last purpose (6):
  - Balance-correction responses allowing for automatic responses to unexpected perturbations of the body's center of gravity.
  - Balance-stabilizing responses allow for the volitional control of the movement of the center of gravity of the body.

### Ocular Motor Control and Perceptions of Motion

The membranous labyrinth is housed within the bony labyrinth in the petrous portion of the temporal bone, where it is secured by connective tissue and is bathed in perilymph. Endolymph is contained within the membranous structure, where the specialized sensory neuroepithelium is located. The vestibular apparatus consists of two groups of specialized sensory receptors: (a) the three semicircular canals—lateral (or horizontal), posterior, and superior, and (b) the two otolithic organs—the utricular macula and the saccular macula, both located in the vestibule. The canals and otolith organs are organized into functional pairs. The two members of each pair are in parallel planes of orientation and function in a 'push / pull' manner. Therefore, if one member of the pair is stimulated by a head movement, the other member is inhibited in its neural activity. The function of the semi-circular canals is to be responsive to angular acceleration and deceleration of the head. The otolith organs are responsive to linear acceleration and deceleration, which includes the force of gravity.

Contiguous with the vestibular portion of the membranous labyrinth is that of the auditory structure, the cochlea. Also housed within the petrous portion of the temporal bone the cochlea shares the same perilymph and endolymph fluids with the vestibular end-organ. It is these structures, the vestibular and auditory portions of the labyrinth, their innervating neural elements (VIIIth cranial nerve, auditory and vestibular divisions) and the motor and sensory nerves for facial expression and taste (VIIth cranial nerve that traverses through this portion of the temporal bone) which are in harms way from temporal bone fractures following head injuries.

Acceleration or deceleration movement of the head, producing stimulation of one or more of the receptors on one side with corresponding reduction of neural stimulation (inhibition) on the other side, results in asymmetrical neural input from the vestibular nerves. This asymmetrical input is interpreted by the central nervous system as either angular or linear movement. In addition, the asymmetry resulting from action of the semicircular canals causes a compensatory reflexive eye movement in the plane of the canals being stimulated. This compensatory reflex movement of the eye is called the vestibulo-ocular reflex (VOR), and is opposite to the direction of acceleration. It is the VOR from the semi-circular canals or the otolith organs that is the basis for the primary function of the vestibular end-organ, stabilization of the visual scene while the head is in motion (1, 2, 5). While there is top down control of the peripheral vestibular and auditory systems, this is especially true for the vestibular mechanism. This control is dominated in the brain stem and cerebellum, but cerebral influence can be easily demonstrated (1, 2).

### Postural and Motor System Control

The cerebral cortex influences lower motor centers via projections through two pathways. The first are long fibers of the corticospinal tract (the pyramidal system), which plays a major role in the control of fine, isolated, versatile movements that set the basis for skill acquisition. The second pathway for cerebral cortex projections is the extra-pyramidal system. These extra-pyramidal pathways provide the mechanisms for large gross movement patterns that are primarily reflexive and constitute major postural adjustments. The pyramidal and extra-pyramidal systems are not independent but must function in a coordinated fashion. The skilled movements of the pyramidal system that are non-postural in nature typically require that a coordinated postural adjustment accompany the smooth skilled movement such as picking up an object from directly in front of the subject while standing. This requires a shift in the overall position of the center of gravity just prior to the arm reach and the grasping of the object by the hand.

Three tracts originate from, or are heavily contributed to via, the vestibular nuclei: the medial and lateral vestibulospinal tracts, and the reticulospinal tract. Given the projections from the medial vestibular nucleus to both the ascending and descending portions of the medial longitudinal fasciculus (MLF) in the medial vestibulospinal tract, this tract may play a major role in the cervical-vestibulo-ocular reflexes, coordinating eye-head movements. Similarly, by examining the inputs to the various areas in the vestibular nucleus and the pathways from those areas to the lateral vestibulospinal and reticulospinal tracts, it is suggested that these have greater

influence on the coordination of head and upper body movement with the lower limbs. It is clear that both the central and peripheral structures participate in the tasks of postural control and ambulation. The organization of this cooperative effort, and its normal functioning during routine daily activities is beyond the scope of this chapter, but available from other sources (7–9).

### Central Vestibular Compensation Process

The vestibular system is the only special sensory system in which unilateral loss of function can seriously threaten the long-term survival or well-being of an organism. In humans, injury to the central or peripheral system may result in considerable disability. Fortunately, most disease processes involving the vestibular labyrinth are self-limited, and spontaneous functional recovery can be expected. This is due to the remarkable ability of the central nervous system to recover after a labyrinthine injury, a process known as vestibular compensation. Failure to recover from a peripheral labyrinthine insult may be due to ongoing fluctuating condition in the vestibular end-organ itself or to failure of central vestibular compensation. Being alert to this critical distinction and its clinical implications is crucial for successful management of the dizzy patient (10, 11). The underlying foundations for this process will be discussed in detail in the second half of the chapter.

## SOURCES OF BALANCE AND DIZZINESS COMPLAINTS AFTER A TBI EVENT

Combinations of specific disorders resulting from a head injury can occur, but for the purposes of this discussion the most common entities will be considered individually. For all of the disorders of the peripheral or central systems, the temporal course of the symptoms (length of spells or events if symptoms are not continuous), and the nature of the symptom onset being spontaneous or provoked by head or visual motion and whether hearing loss is involved with the symptoms are the key features of the history. The history, as with other patients complaining of dizziness or imbalance, is the single most important evaluation tool for the investigation of the cause of the complaints. For each of the encapsulated description disorders below these features will be reported.

### Disorders of Peripheral Vestibular Origin

Post-traumatic injury to the peripheral vestibular system can occur in isolation or in association with a hearing loss. In cases where clear indications for peripheral vestibular involvement is lacking, but suspected, the presence of a documented post injury hearing loss adds significantly to the argument for peripheral dysfunction.

*Benign Paroxysmal Positional Vertigo* This is considered one of the most common causes for complaints of dizziness (vertigo) and imbalance, and the most common source for dizziness post head trauma. It is characterized by brief spells (typically <1 minute) of vertigo, falling or lightheadedness provoked by a movement of the head. In the most common form of this disorder, the provocative movements are in the saggital plane. The provoked symptoms are very frequently accompanied by complaints of general imbalance during daily routines. The character of the disorder is to have it resolve spontaneously and then recur. The length of time for symptoms can vary from as short as a single day to greater than 1 year. Resolution length has equally as large a variance. This is a disorder of the inner ear where the semi-circular canals, which are not sensitive to the pull of gravity, have an altered mechanics that make them sensitive to gravity. This occurs secondary to suspected displacement of crystal structures from the otoliths into the semi-circular canal system. Hearing loss is not a typical feature associated with this disorder, but certainly could occur given head trauma as the precipitating source. Treatments are highly successful and typically consist of head maneuvers referred to as ‘canalith repositioning procedures’ during which the crystal structures are repositioned out of the involved canal (see below) (12–17).

*Labyrinthine Concussion* This disorder is characterized by hearing loss and vertigo both of sudden onset following a head trauma. The symptoms typically improve over days and in many cases some recovery of hearing may occur. Usually the symptoms of continuous vertigo resolve into being present only when provoked by head movements in any direction. It is thought that the violent movement of the fluids and tissues within the inner ear can cause tearing of tissues and / or set up a series of events where metabolically the cells undergo deterioration and death. This condition occurs in the absence of a documented fracture of the temporal bone (18). Secondary to the typical long-term symptoms of head movement provoked brief spells (seconds to minutes <5) these patients are good candidates for management with vestibular and balance rehabilitation therapy. Suppressive medication is many times needed at the initiation of this condition to control the sudden onset of vertigo and associated neurovegetative symptoms (19, 20).

A long term consequence of damage to the vestibular labyrinth, independent of the etiology, is the development of spontaneous spells of vertigo lasting minutes to hours. In some cases these can be associated with fluctuant or progressive hearing loss in a format classic for Meniere’s disease. However, this is considered a secondary Meniere’s resulting from the previous trauma. When it takes the form of only the spells of vertigo without associated auditory symptoms the older term is that

of post-traumatic endolymphatic hydrops. If the symptoms involve only the spontaneous events, vestibular and balance rehabilitation therapy is typically not applicable and the treatment options are the same as those used in cases of Meniere's of idiopathic origin (21).

**Temporal Bone Fractures** Both blunt and penetrating trauma to the temporal bone can lead to damage to the ear or VIIIth nerve complex. These injuries may result in a conductive hearing loss secondary to trauma to the external and/or middle ears, or a sensorineural hearing loss secondary to labyrinthine or VIIIth nerve trauma. Vertigo and subsequent imbalance may occur as an isolated symptom, or may be associated with a sensorineural hearing loss.

Approximately 75% of head injuries occur in motor vehicle accidents, with approximately 20% of these patients displaying some symptoms related to temporal bone trauma (22, 23). Thus, motor vehicle accidents are the most common cause of blunt trauma to the temporal bone (45%) with falls (20%), altercations (10%), and athletic injuries (10%) accounting for the majority of the remaining injuries.

Penetrating trauma is a less common cause of temporal bone injury, with etiologic agents for this form of injury ranging from bullets and knives to pencils and cotton swabs.

Temporal bone fractures elicited by blunt trauma have classically been defined by the relationship of the axis of the fracture line to the long axis of the temporal bone. Thus, longitudinal fractures, course along the external auditory canal, through the tegmen of the middle ear, and then pass anterior to the labyrinth to terminate in one of the foramina (lacerum or spinosum).

Transverse fractures run perpendicular to the long axis of the temporal bone, traversing the petrous bone between the foramen magnum and the foramen spinosum or lacerum, typically disrupting either the bony labyrinth or internal auditory canal. More recent data indicate that most temporal bone fractures possess properties of both longitudinal and transverse fractures, and are thus classified as mixed or oblique fractures. Projectiles may involve any or all components of the temporal bone, depending on their trajectory. More benign penetrating objects (e.g. pencils, cotton swabs), may elicit neurovestibular symptoms by disrupting the interface between the stapes and the labyrinth, creating a perilymph fistula (see below).

Trauma to the external canal manifests with bloody otorrhea and severe pain. A traumatic tympanic membrane perforation will have a similar presentation, with hearing loss always being present. Disruption of the ossicular chain most commonly involves the incus and results in a persistent conductive hearing loss. Disruption of the stapes may result in a conductive, mixed, or profound hearing loss (see perilymphatic fistula below).

The hallmark of a labyrinthine injury secondary to blunt or penetrating trauma is the presence of vertigo and hearing loss. In cases of severe head injury, in which the patient has been comatose for a period of time, the symptom of vertigo may be supplanted by the complaint of imbalance. Fractures that approximate a longitudinal course do not cause a direct disruption of the inner ear or VIIIth nerve. However, patients may suffer both sensorineural hearing loss and vertigo secondary to what has been referred to as a *labyrinthine concussion* (see above). In this situation, the vertigo is typically acute and self-limited, and the hearing loss is, at least partially, reversible. In contrast, fractures that traverse the otic capsule or internal auditory canal will cause profound hearing loss and vertigo.

Signs on physical examination indicative of inner ear trauma include tuning fork tests that lateralize to the unaffected ear and spontaneous nystagmus consistent with either an irritative (toward the affected ear) or parietic (away from the affected ear) lesion.

Audiometric assessment will define the nature of the hearing loss (conductive, sensorineural, mixed) and vestibular testing will document a vestibular injury. High resolution CT scan of the temporal bone is indicated to define the nature of the fracture and the structures involved.

External canal trauma should not be manipulated at initial presentation, as a traumatic dural or brain exposure may be present. Once CT scan has ruled-out these complications, the ear should be gently microdebrided and attempt made to reposition any avulsed pieces of skin. A post-traumatic ear canal stenosis may occur which will require surgical repair, both to improve hearing and prevent cholesteatoma formation secondary to the presence of squamous epithelium trapped medial to the stenosis. Tympanic membrane perforations should be managed conservatively as the rate of spontaneous healing is close to 100%. Disruption of the incus will require an ossiculoplasty once the primary healing process is completed (6 weeks to 3 months).

Other than for a perilymph fistula (see below), no specific treatment exists for blunt or penetrating inner ear trauma. Vestibular suppressants can be used for acute vertigo control, if not otherwise contraindicated by the patient's overall medical status. Hearing aid amplification may be useful in patients with partial sensorineural hearing loss, and vestibular rehabilitation therapy is indicated in those patients with a slow recovery from their vestibular loss.

The majority of patients sustaining temporal bone injuries develop little or no inner ear dysfunction. Patients who do sustain a noncompensated vestibular loss generally respond well to vestibular rehabilitation therapy. Benign paroxysmal positional vertigo (BPPV) is a common sequela of head injury and is in fact, the most common form of post-traumatic vertigo. Any patient complaining of

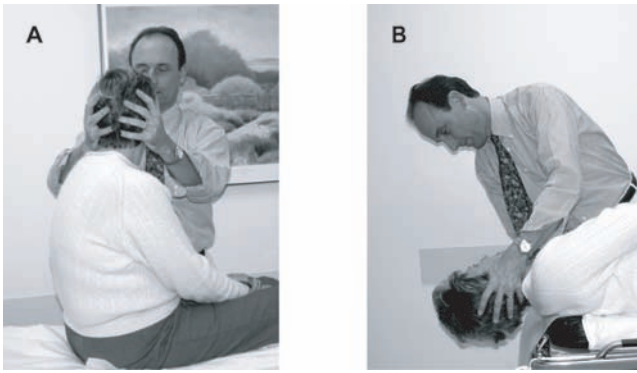


FIGURE 28-1

The left Dix-Hallpike Test. (A) The patient sits with legs extended on the table and cervical spine rotated 45 degrees to the left. The examiner places his hands on either side of the patient's head, with his right fore-arm behind the patient's left shoulder. (B) The patient is quickly brought into supine and the cervical spine extended approximately 10 degrees. The examiner observes the patient for nystagmus and symptoms

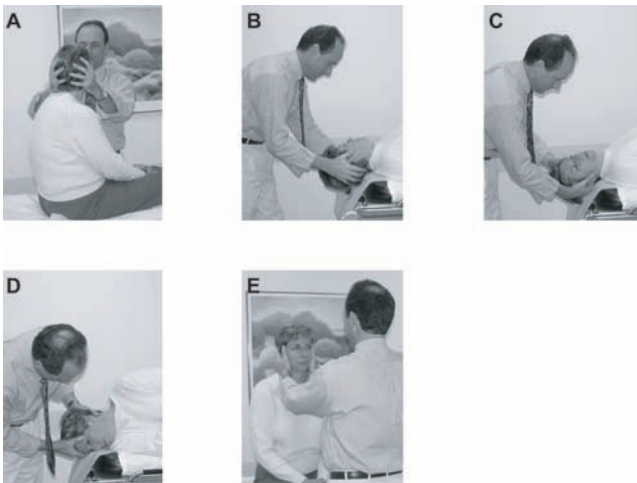


FIGURE 28-2

The Canalith Repositioning Maneuver for left-sided BPPV. (A) The starting position is identical to the initial position in the Dix-Hallpike test, with the cervical spine rotated 45 degrees to the left. (B) The patient is brought into supine and the cervical spine is extended approximately 10 degrees (45 degrees of left cervical rotation is maintained). (C) The cervical spine is rotated 90 degrees to the right to end up in 45 degrees rotation to the right. (D) The patient is rotated onto their right side, maintaining the cervical rotation to the right. The cervical spine is brought out of extension, and is laterally flexed to the right. (E) The patient is brought into sitting. As the patients rises from right side lying to sitting, the cervical rotation to the right is maintained

vertigo after a head trauma should have a Dix–Hallpike maneuver performed in the office (see Figure 28-1). If the diagnosis of BPPV is confirmed, then an canalith repositioning maneuver (see Figure 28-2) should be performed.

This therapeutic maneuver is highly efficacious and greatly appreciated by the patient.

**Perilymphatic Fistula** A Perilymph Fistula (PLF) occurs when the boundary between the middle and inner ear has been violated, allowing egress of perilymph and inner ear dysfunction. The topic of PLF remains controversial, particularly with respect to the spontaneous variety.

Perilymph fistulae are proposed to occur via three possible mechanisms. Congenital inner ear anomalies involving the otic capsule may result in dehiscences in the labyrinth that allow communication between the middle ear and the labyrinthine fluids. These are typically children who present with severe to profound hearing loss and recurrent meningitis or CSF leak (24).

More relevant to this discussion is the development of a PLF due to disruption of the oval (or less commonly, round) window secondary to external trauma. This trauma may be iatrogenic (e.g. post-stapes surgery) or secondary to blunt or penetrating trauma. Barotrauma and acoustic trauma have been proposed to create fistula via the transmission of rapid pressure changes to the round and oval windows (so called “implosive trauma”) (25). However, as indicated above, these forms of trauma rarely result in a frank PLF.

Most of the controversy pertaining to PLF surrounds the spontaneous variety. This is proposed to occur through leaks through congenital dehiscences in the otic capsule, typically occurring in the regions of the oval and/or round windows. The leak through these dehiscences was thought to be precipitated by an increase in intracranial pressure being transmitted to the inner ear (“explosive trauma”) (25). The validity of the concept of a spontaneous perilymph fistula has been critically scrutinized by otologists over the past two decades with a consensus emerging amongst most authorities that spontaneous fistulae rarely, if ever, occur (26–28).

A wide gamut of symptomatology has been ascribed to the PLF. Currently, most otologists would consider the diagnosis of a fistula when a patient presents with a sudden sensorineural hearing loss associated with tinnitus and vertigo, occurring immediately subsequent to a traumatic insult. Fluctuations in hearing may support the diagnosis if they appear provoked by pressure fluctuations or straining.

Despite intense effort no valid and accurate diagnostic test for PLF exists. A fistula test, in which a pressure change is applied to the inner ear via a pneumatic otoscope or tympanometer, may be considered positive if it evokes symptoms and nystagmus. However, this test is nonspecific and may also be positive in Meniere’s disease and otosyphilis. Audiovestibular testing, including electrocochleography, do not reveal any pathognomonic findings. Detection of fluorescein in the middle ear subsequent to intravenous or intrathecal injection has not



proven to be clinically useful. Similarly, the detection of beta2 transferrin in the middle ear has not proven to be an accurate method of identifying a PLF (29).

Most authorities agree that the only manner in which the presence of a PLF can be confirmed is by direct observation of the leakage (30). Based on recent results, it would appear that the most accurate way of performing this exploration is by using endoscopes passed through a myringotomy incision (31, 32). This technique appears to avoid false positive results that occur secondary to pooling of fluid, such as anesthetic injection, during the raising of tympanomeatal flap.

Bed rest, head elevation, and avoidance of straining are the initial treatments employed when a PLF is suspected. If symptoms of fluctuations of hearing and/or vertigo persist for 2–3 days while on this treatment regimen, a middle ear exploration and patching of the fistula site (oval and/or round window) should be considered.

In one study, 68% of patients with identifiable fistulae at the time of exploration improved after patching of the fistula (30). The majority of these patients had undergone previous stapes surgery. In patients who sustain a frank stapes subluxation subsequent to an external trauma, the prognosis is more guarded for recovery of auditory function.

### **Central Nervous System Causes for Balance and Dizziness**

There are multiple sources of injury and secondary disorders to head trauma that can originate in the central nervous system and manifest in symptoms of balance and dizziness. Both post-traumatic seizures and post-traumatic stress syndrome / anxiety disorders can be direct causes for complaints of symptoms ranging from vertigo to vague lightheadedness and imbalance. Mechanisms, investigation and treatment for these entities are considered elsewhere in this text and will not be repeated herein. It is important to realize that there can be dramatic effects of psychological disorders that develop with long term disorders and are expressed in the complaints of dizziness (33–35).

Direct trauma to the brain stem and / or cerebellum will result in complaints of imbalance with standing and walking and occasional complaints of true vertigo. The pathophysiology of injuries of this nature is addressed in another chapter in this text. The nature of the signs and symptoms will vary depending on the location of the lesion within the central nervous system (36). Lesions within the brain stem and cerebellum have typical ocular motor abnormalities that can be recognized during the office or laboratory examinations of these patients (see discussion below). Given that these are typically stationary lesions vestibular and balance rehabilitation therapy will comprise a major portion of the treatment plan.

These are usually not spontaneous events of symptoms but are more likely to be continuous sensations of disorientation, and imbalance with gait (37).

Post-traumatic migraine headaches, as with non-traumatic migraines, can have dizziness as an aura for the migraine event. This can occur with or without the pain phase of the migraine event. When the events of dizziness are not temporally related to actual headaches this entity can be quite difficult to diagnosis as it has to be a diagnosis of exclusion. Symptoms from migraine associated dizziness can be spontaneous spells of true vertigo to vague complaints of increased sensitivity to motion sickness and anything in between. Recognition of this is typically accomplished by having a history that the headaches being experienced meet the criteria for migraine, or pre-trauma the patient had a migraine history. Once diagnosed these are treated by direct treatment of the headaches (38, 39). In some cases the patient can be assisted with the use of vestibular and balance therapy as long as there is simultaneous focused treatment on the underlying migraine disorder.

In addition to the above descriptions of the direct effects of the central nervous system lesions producing symptoms of dizziness and imbalance, all of the above can have an indirect effect as well. In patients with combined peripheral and central lesions, the presence of the central lesion in the brain stem and / or cerebellum may not be causing direct symptoms of dizziness or imbalance but could cause disruptions in the natural central system compensation process. This would have the effect of slowing or preventing the compensation process from reducing the symptoms from the peripheral vestibular insult. This disruption in the compensation process can also occur from psychological difficulties, migraines or seizure disorders. In these instances direct treatment for the other disorders would be necessary in order to allow for as full a compensation process as possible.

### **OVERVIEW OF ASSESSMENT TOOLS AND THEIR USE IN DIAGNOSIS AND TREATMENT**

Even though a head injury with TBI may be the precipitating event that results in complaints of imbalance and dizziness, one must proceed in the evaluation of those complaints in a systematic manner to uncover the source of the symptoms. Therefore, the evaluation is not different from what would be performed for a patient presenting without a known antecedent event. In considering the evaluation of the patient with complaints of vertigo, lightheadedness, imbalance or combinations of these descriptors, one must look beyond just the peripheral and central vestibular system with its ocular motor connections. The various pathways involved in postural control, only part of which have direct or indirect vestibular input should be

kept in mind during an evaluation. The event that produced the head injury could easily have caused injury to any of these postural control pathways independent of the resultant TBI. Additionally, significant variations in symptoms and test findings can be generated by migraine disorders (37, 38) and / or anxiety disorders (33–35), yet these are diagnosed primarily by history requiring a specific line of questioning.

The evaluation of the dizzy patient should proceed being guided by what information is needed to make initial and subsequent management decisions. When various tests are reviewed, and correlated with high level activities of daily living, virtually no significant relationships exist for the chronic dizzy patient. Tests considered extent and site-of-lesion studies, Electronystagmography (ENG), Rotational chair and specific protocols in postural control assessment (5, 40), give results that are unable to be used to predict symptom type, magnitude or the level of disability of an individual patient. Conversely, patient complaints can not be used to predict the outcomes of these tests (41–44). In a limited manner more functionally oriented evaluation tools, computerized dynamic posturography (CDP), dynamic visual acuity testing (45) provide for some correlation between results, patient symptoms and functional limitations. Add to the testing specific or general health inventories like the Dizziness Handicap Inventory (41) and predictive assessment of disability is improved but remains significantly limited. It is hypothesized that the reason for this dichotomy in test results versus functional disability and symptom complaints is the inability of the tests to adequately characterize the status of the central vestibular compensation process (5, 46). It is the exception, not the rule that vestibular and balance laboratory tests return results that would drive management of the dizzy patient. It would be extremely rare that these studies return a diagnosis. Therefore, the routine use of these tools to determine how to proceed with the management of a dizzy patient is a false line of reasoning and not productive in the majority of the patients. In general the laboratory studies are productive in determination of extent and site-of-lesion within the peripheral and central vestibular system and the functional limitations in static and dynamic postural control (44). The use of this information is in the confirmation of the suspected site-of-lesion and diagnosis derived from patient history and direct physical office vestibular evaluation.

To summarize the above discussion, the following are required elements to management decisions for the chronic dizzy patient; detailed neurotologic history, office vestibular and physical examination, and formal audiometric testing given the inescapable anatomical relationship between the auditory and vestibular peripheral systems. The following are considered important, however less likely to directly drive the management in the typical

case; laboratory vestibular and balance-function studies, neuroradiographic evaluations and serological tests. It is important to realize that there will be patients for whom unexpected findings on any one of these latter studies will either alter the complete course of the management or add dimensions to the management not originally considered. But for the majority of patients the vestibular and balance tests will be confirmatory in nature.

The following discussion will be a very brief overview of the major elements available for assessment. A recent comprehensive summary of the evaluation of the dizzy patient and detailed descriptions are found elsewhere for the interested reader (5, 9, 40, 44, 47).

### Neurotologic History

Given the various tools for assessment, the history is the single most important factor in determining the course of management, and therefore requires discussion. The differentiation between the various peripheral vestibular disorders, that can result from a head injury, is particularly dependent upon historical information and the conclusions that the physician draws from the interview. Most vestibular disorders cannot be distinguished from one another simply by vestibular testing or other diagnostic interventions. Failure to properly discriminate these disorders on historical grounds may lead to improper management by the physician. In addition, balance function study results are best interpreted in light of a proper clinical history.

It is very important to question the patient regarding the association of a hearing loss or other auditory symptoms with the onset of vertigo. A complete audiometric assessment should be performed early in the evaluation. The presence of an associated sensorineural hearing loss, whether stable, progressive, or fluctuating, is the single strongest incriminating factor in identifying a pathologic labyrinth. The presence of other otologic symptoms such as aural fullness and tinnitus may also be helpful in lateralization. The features in the history will be the primary determiners of the initial choice for treatment (see Management Options sections below).

### Office Examination

A variety of test procedures may be used in the office setting to assess the balance-disorder patient. These, like the laboratory studies, assist in the identification of the extent and site of the lesion. These straight-forward clinical tests are essentially variations of the related laboratory studies, but have less ability to quantify the outcomes. The theoretical basis behind many of these tests is well founded in the physiological considerations discussed above and in the references provided. Due to the subjective nature of these tools, the validity and reliability of these tests are reduced compared to the formal laboratory studies.

It is important that the person evaluating the dizzy patient be aware that simple tools do exist which provide for an effective evaluation. In the majority of patients this evaluation produces the same impressions as the extensive laboratory studies discussed below. These tools are, however, not as sensitive to mild anomalies as the laboratory studies. A recent summary of these techniques is available in the literature (9).

### Laboratory Studies

*Electronystamography (ENG)* Traditional ENG, using electrodes placed around the eyes or infrared video techniques for eye movement recordings, is a process that estimates the position of the eye as a function of time. Since the primary purpose of the vestibular apparatus is to control eye movements, the movements of the eyes may be used to examine the activity of the peripheral vestibular end organs and their central vestibulo-ocular pathways. The ENG evaluation is a series of sub-tests performed to assess portions of the peripheral and central vestibular systems. It is important to understand that peripheral vestibular system assessment with ENG is significantly limited, typically reflecting function of the horizontal semicircular canal with restricted information from vertical canals and otolith organs. With the use of computerized ENG systems, which afford significant visual stimulus control and quantitative analysis, evaluation of the central vestibulo-ocular pathways can be quite thorough.

*Rotary Chair* Rotary chair testing has been used to expand the evaluation of the peripheral vestibular system. As with the ENG findings, the rotational chair evaluation can assist in site-of-lesion determination, counseling the patient and confirmation of clinical suspicion of diagnosis and lesion site, but is not likely to significantly alter or impact on the course of patient management, excepting the bilateral peripheral weakness patient.

As with the ENG, electrode or video techniques are used to monitor and record the outcome measure of interest, jerk nystagmus, that is generated in response to the angular acceleration stimulus produced by the circular movements of the chair.

*Postural Control Assessment* Just as all patients that are being evaluated in the laboratory need tests for peripheral and central vestibulo-ocular pathway involvement, they also require some assessment of postural control ability. There are several different general approaches to formal postural control testing, each with specific technical equipment requirements and goals for the testing (5, 48). Briefly, the most common equipment detects vertical and horizontal forces from the feet by two independent force plates upon which the subject stands. Three principle testing

protocols are used in patient evaluation, the Sensory Organization Test (SOT), the Motor Control Test (MCT) and Postural Evoked Responses (PER). These allow for assessment ranging from strictly functional (not site-of-lesion) with the SOT to site and limited pathology specific results with PER. Because of the functional assessment using SOT, postural control assessment is useful in the development and monitoring of vestibular and balance rehabilitation management option discussed below.

### OVERVIEW OF TREATMENT OPTIONS

The options for management of the dizzy and balance-disordered patient fall into the major categories of medication, surgery, dietary changes and vestibular and balance rehabilitation therapy (VBRT), or combinations of these techniques (5). In general it will be the rare patient with dizziness secondary to head injury that is going to be managed with medication alone. The most common use of medications in this arena would be short term or 'as needed' use of vestibular suppressant medications for acute symptom control at the onset or with recurrent spontaneous events of vertigo lasting hours. Other than migraine and psychological disorders there is little call for use of chronic medication. Of the medications most commonly used for vestibular suppression the primary classes are those of antihistamines (Meclizine & Promethazine), anticholinergics (Scopolamine), phenothiazine (Prochlorperazine) and benzodiazepines (Diazepam, Lorazepam & Clonazepam). There are other classes and other specific medications within these listed drug classes that have been used for the control of acute vertigo and the vegetative symptoms that accompany the sensation of vertigo. It is important to remember that use of these medications should be on a short term basis and only 'as needed' when possible. These classes of medications have an effect that can significantly slow the natural compensation process and the effectiveness of VBRT (17).

Surgical intervention for this group of patients is used even less frequent than medication. The patients for whom surgery may be considered are those discussed above associated with temporal-bone injuries and perilymphatic fistulas. The treatment option that would be the most common is VBRT. This option will be discussed in detail below.

The major feature that drives an initial decision as to the use of medication / surgery versus VBRT is the evidence that the peripheral or central vestibular lesion is unstable (varying over time), as opposed to an uncompensated stable lesion. This distinction comes dominantly from the patient's presenting symptoms. Therefore, the patient should be asked to describe the progression of symptoms over time, along with the nature and duration of typical spells. Specifically, one wishes to know if the

symptoms are continuous or occur in discrete episodes. If the symptoms are episodic, it is extremely important to distinguish whether they are spontaneous or motion-provoked. If the symptoms are brief and predictably produced by head movements or body position changes, the patient most likely has a stable lesion, but has not yet completed central nervous system compensation. Those who describe these symptoms sometimes also note a chronic underlying sense of disequilibrium or lightheadedness. The chronic symptoms may be quite troublesome, but any intense vertigo should be primarily motion-provoked. These patients are suitable candidates for vestibular rehabilitation. It is important to point out that historical information is essential in deciding who might benefit from rehabilitation therapy.

If the episodic spells described by the patient are longer periods of intense vertigo that occur spontaneously and without warning, this is probably a progressive or unstable peripheral dysfunction. One must also suspect a progressive lesion if the vertigo is accompanied by fluctuating or progressive sensorineural hearing loss. Such patients are managed with medical therapy, and if this fails, they constitute the best candidates for surgical intervention. Such patients are not candidates for vestibular rehabilitation, except as an adjunctive modality. For the chronic patient, including those with known head trauma event, the primary effort is to determine why they have not had the natural central compensation process run to completion.

When dealing with the TBI patient group, VBRT is many times used as one component of a comprehensive traumatic brain injury rehabilitation program involving physical, occupational, speech and cognitive therapy aspects.

### **VESTIBULAR AND BALANCE REHABILITATION THERAPY PROGRAMS**

As indicated above, VBRT is the most frequently used management option for patients with balance and dizziness complaints from head injury, or other causes. Therefore, the remainder of this chapter will be a detailed discussion of this technique.

Since traumatic brain injury can lead to damage of the vestibular system from peripheral to central structures, as well as cause other CNS damage, the types of exercises used to treat the dizziness and imbalance can be quite comprehensive. The aims of the following sections of this chapter are to 1) review the rationale behind vestibular and balance rehabilitation therapy (VBRT), 2) identify the types of problems that can be treated with VBRT, 3) describe the various types of exercises used in VBRT, 4) discuss modifications of treatment programs for individuals with traumatic brain injury, and 5) describe the outcomes to date.

The use of exercise for the treatment of individuals with vestibular dysfunction is not new. In the 1940's Sir Terrence Cawthorne, an otolaryngologist, and F. S. Cooksey, a physiotherapist, devised a series of exercises for the treatment of individuals with unilateral vestibular paresis and post-concussion syndrome (49–51). Cawthorne and Cooksey realized that head movements often provoked an individual's symptoms of dizziness. They also observed that patients who were active recovered faster and hypothesized that head movements must be important in the recovery of function. Their initial exercise program consisted of a variety of eye, head, and body movements to habituate the dizziness. Since the development of those exercises, several other approaches to the treatment of patients with complaints of vertigo and dysequilibrium have been described. These exercises generally fall under four different categories, exercises to promote habituation, exercises to promote adaptation, exercises to promote substitution, and exercises designed to treat benign paroxysmal positioning vertigo. Any of these exercise approaches may be indicated in an individual with dizziness secondary to traumatic brain injury. The challenge to those treating these individuals is to identify the nature of the cause of the dizziness and to design the appropriate treatment programs.

Habituation exercises, like those described initially by Cawthorne and Cooksey, are based on the principle that repeated exposure to a noxious, or provocative, stimulus (in this case movements) will lead to a reduction in the body's response to that stimulus.

The exercises to induce adaptation of the vestibular system, while similar to the approaches mentioned above, reflect our increased knowledge of the function and adaptation of the vestibular system. Adaptation exercises are designed to promote long term (plastic) changes in the neuronal response of the vestibular system to a given head movement, with the goals of decreasing retinal slip, improving postural stability, and decreasing symptoms. These exercises are typically used in individuals with an uncompensated unilateral vestibular loss. The treatment approach for individuals with unilateral vestibular hypofunction differs in both theory and practice from the approach for individuals with bilateral vestibular loss. For individuals with bilateral vestibular loss, exercises to promote the substitution of alternative strategies for gaze stability and postural control are appropriate.

Finally, the exercises to treat BPPV are based upon the hypothesis that there are crystalline structures, which are consistent with degenerating otoconia from the otolithic membrane (52). These crystals cause an abnormal mechanical stimulation of the vestibular system with changes in head position relative to gravity. These exercises, while simplistic in the current arena of high tech medicine, are very effective in alleviating the signs and symptoms of BPPV. Benign Paroxysmal Positioning

Vertigo can occur in conjunction unilateral vestibular loss, central vestibular disorders, and in some cases with bilateral vestibular loss. Consequently, the treatment of BPPV is often combined with other exercise approaches to treat the identified problems. Determination of the appropriate exercise program rests on the findings of the clinical examination and available vestibular function tests.

### **Who Is an Appropriate Candidate for Vestibular Rehabilitation?**

Generally, individuals with stable vestibular function and symptoms provoked by head motion (either self-motion or motion in the environment) or environmental situations (e.g. absence of visual cues, altered somatosensory cues) will benefit from vestibular rehabilitation. Individuals with vestibular function that fluctuates, as in Meniere's disease, or those who have true spontaneous episodic bouts of dizziness, typically will not benefit from vestibular rehabilitation.

### **Treatment of Individuals with Benign Paroxysmal Positioning Vertigo**

Benign Paroxysmal Positioning Vertigo (BPPV) can affect any of the three semicircular canals, although the most commonly encountered presentation is that of posterior canal BPPV (53). In addition, the BPPV is thought to be caused by one of two mechanisms, cupulolithiasis (54) or canalithiasis (55, 56). In canalithiasis, the otoconia are mobile in the long arm of the semicircular canal; in cupulolithiasis, the otoconia are adherent to the cupula. The effect, in both cases, is to make the involved canal sensitive to the pull of gravity. The presentation of the two types of BPPV differs, as do the treatments for each condition. The methods used to determine the involved canal and the nature of the BPPV as well as a comprehensive review of the various treatment techniques are beyond the scope of this chapter. The interested reader is referred to the following articles for review (57, 58). Identification and treatment of posterior canal canalithiasis, the most common form of BPPV encountered in the clinic, will be reviewed here. The test for BPPV is the Dix-Hallpike maneuver (59). To perform this test, the patient sits with their legs extended on the examination table, their cervical spine is rotated approximately 45° to one side, their head is supported in the examiner's hands, and they are quickly brought into supine, with the cervical spine extended 10° to 20° and the head hanging off the table (see Figure 28-1). The patient is held in this position for up to 60 seconds, and the eye movements and the patient's symptoms are monitored. In a patient without BPPV, this test will produce no vertigo and no nystagmus. In a patient with BPPV, the Dix-Hallpike test will provoke both vertigo and a mixed vertical-torsional nystagmus.

The fast phase (beat) of the vertical component of the nystagmus will be upwards (relative to the patient). Torsional eye movements are rotations of the eye around the line of sight axis, and the direction of the nystagmus is named for the movement of the superior pole of the eye (again relative to the patient) during the fast phase of the nystagmus. The torsional component of the nystagmus will beat towards the involved ear, which is generally the dependent ear in the Dix-Hallpike maneuver. The nystagmus and vertigo will be present less than 2 minutes, and will generally persist for 30 seconds or less. The observed nystagmus and vertigo are due to an abnormal stimulation of the posterior semicircular canal, presumably due to movement of the otoconia away from the cupula. On arising to sitting, there is often a recurrence of the vertigo and a reversal of the nystagmus. This reversal of the nystagmus is due to the otoconia now moving back towards the cupula of the semicircular canal.

Treatment of this form of BPPV is straightforward. John Epley (60) first described a series of positioning maneuvers designed to move the offending otoconia out of the involved canal. Others have modified his procedure by altering some of the movements, changing the time in each position, and not using a mastoid vibrator during the treatment. This modified procedure is typically referred to as the canalith repositioning maneuver (CRM) or canalith repositioning procedure (CRP) (57, 61, 62). For the following description of the maneuver, we will assume that the patient has left-sided, posterior canal canalithiasis. If the patient had right-sided, posterior canal canalithiasis, the direction of the rotations would be reversed. To begin the CRM, the patient is long sitting on a treatment table, with the cervical spine rotated 45° to the affected side (Fig. 28-2A). The patient, whose head is supported by the examiner, is then brought into supine, and the cervical spine is extended 10° or 20° (Fig. 28-2B), and this position is maintained for 30 seconds to 2 minutes. The patient's neck is then extended further (if possible) and then rotated 90°, so that the final position is 45° rotation to the right (Fig. 28-2C). This position is maintained for 30 seconds to 2 minutes. The patient then rolls onto the right side, maintaining the same degree of cervical rotation. During this rotation of the body, the cervical spine is brought into neutral with respect to flexion and extension and laterally flexed to the right, to bring the head down toward the treatment table (Fig. 28-2D). This position is maintained for 30 seconds to 2 minutes. The patient is finally brought to into sitting from the side lying position, maintaining the cervical rotation until the patient is upright (Fig. 28-2E). The time spent in each position varies among practitioners. Epley (60, 63) suggested that each position be held for 1.5 times the duration of the nystagmus observed in the Dix-Hallpike test. Post-treatment instructions to the patient also vary among practitioners. Some suggest that the patient remain

upright for 24 hours post-treatment; while others will retest the patient to determine the efficacy of the treatment. If one elects to re-assess the patient after the initial treatment, then one should repeat the treatment even if the post-test is negative. The treatment is repeated to avoid the possibility of having the otoconia move back into the affected semicircular canal during the re-assessment. Following successful treatment, patients are generally instructed to perform the CRM or Brandt-Daroff exercises at home in an attempt to prevent a recurrence of the BPPV.

### Treatment of Gaze Instability

One of the primary functions of the vestibular system is to generate compensatory eye movements to a given head movement, the vestibulo-ocular reflex (VOR). The VOR, when functioning appropriately, allows the individual to maintain the object of interest on the fovea, thereby preserving visual clarity. If the vestibular system is not functioning appropriately, the eye movements generated in response to head movement will not be sufficient to keep the object of interest on the fovea. The resulting movement of the image on the retina, retinal slip, will lead to a degradation of visual acuity. In individuals with remaining vestibular function (for example those with a unilateral vestibular deficit), the exercises are designed to foster adaptation of the remaining vestibular signals to generate the appropriate eye movement responses. For those individuals without vestibular function (for example those with bilateral vestibular loss) there is no remaining vestibular signal to adapt. Consequently, the exercises for these individuals are designed to promote the use of alternative strategies to promote gaze stability during head movements. The two general exercise approaches and the rationale behind the exercises will be explained separately.

*Exercises to Enhance Vestibular Adaptation* The rehabilitation of individuals with unilateral peripheral vestibular hypofunction or loss (UVH) is based upon the plasticity inherent within the vestibular system. The ability of the vestibular system to modify its behavior during development, as well as in disease states, has been well documented (for a review see review by du Lac and colleagues (64)). In the case of an insufficient VOR, due to vestibular hypofunction, the vestibular system will not generate sufficient eye movements in response to head movements. This will cause the visual image to move across the retina. This retinal slip in the presence of head movements appears to be an effective stimulus for inducing adaptation of the VOR (65). For patients with remaining vestibular function, the exercises used in the treatment of gaze stability deficits are designed to generate these error signals and thereby foster adaptation of the vestibular system (66). The goals of this aspect of the rehabilitation program are to 1) improve

visual acuity during head movements, 2) improve visual-vestibular interactions during head movements, and 3) decrease the individual's sensitivity to head movements.

As a consequence of the error signal produced by the exercises, performance of the exercise is frequently associated with symptoms of dizziness or nausea. The patient must be aware that provocation of their symptoms is a necessary part of the rehabilitation process. If there is no symptom provocation with the exercises, then the patient is not challenging the vestibular system and adaptation will not occur. The first exercise to address the gaze instability issue is often called x1 (times one) viewing, since the eye velocity must equal the inverse of the head velocity to maintain visual fixation (Fig. 28-3A). To perform the exercise, the patient fixates on a visual target (a small letter or number) located on a plain visual background, approximately 3 feet away. The patient then rotates his/her head, maintaining fixation on the visual target throughout the head rotation. The image should remain in focus and stable in space. The amount of head rotation should be approximately 30°–45° to either side of midline. The patient should avoid maximum deviation of the eyes as visual acuity decreases in these positions and end gaze nystagmus should be avoided. Cervical range of motion limitations and glasses, especially bifocals, may limit the degree of head rotation. Head rotation, both horizontal and vertical, should be performed as rapidly as the individual can tolerate, with the restriction that the visual target must remain in focus and stationary. Oscillopsia will develop if the velocity of the head rotation exceeds the capacity of the VOR. The exercise should be performed continuously for 1 (initially) to 2 minutes. The duration should be progressed gradually to avoid severe exacerbation of the symptoms or provocation of cervical pain. As the individual improves, the velocity of head rotation can be increased. Altering the postural demands or the visual conditions will vary the stimulus context. If the patient has difficulty with independent stance, then the exercise can be performed initially while sitting. Having the patient stand with a wide base of support on a firm surface increases the postural demand. This condition forces the CNS to utilize somatosensory and visual cues to maintain balance in the presence of fluctuating vestibular signals. As the patient improves, they begin to perform the exercise with a narrower base of support, which is a more challenging position. This gradual reduction in the base of support is continued until the patient can perform the exercise in tandem stance. The exercise can also be performed on a foam cushion to perturb the somatosensory signals. This progression in postural demands occurs over the course of several weeks. On any given day the patient will perform the x1 viewing exercise under only one postural condition.

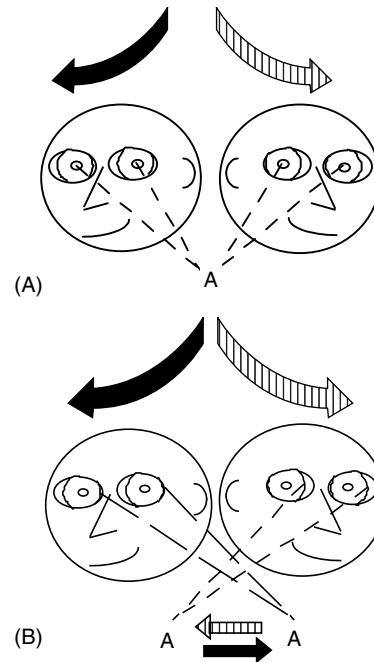
Since adaptation of the vestibular system is context specific, (67) the context of the visual stimulus should vary to reflect the different visual conditions that an individual

normally encounters. The influence of the optokinetic system (parafoveal visual stimuli) on gaze stability can be incorporated into the exercise program by placing the visual target within a “full-field” visual stimulus such as a checkerboard. When the visual target is at the same depth as the full-field visual stimulus, then the optokinetic system will assist the VOR in generating the appropriate compensatory eye movements. If the visual target is in front of the full-field visual stimulus, then the optokinetic system will actually generate anti-compensatory eye movements, since the visual world behind the object of interest appears to move in the same direction as the head movement. Since both of these stimulus conditions are encountered in normal activities, both conditions are incorporated into the rehabilitation program.

When the object of interest is near, the translation of the eyes relative to the visual target is greater than when the target is at a distance. The neural circuitry controlling the VOR normally takes target distance into account when generating the compensatory eye movements. Therefore the x1 viewing exercises are also performed with larger visual targets at a distance (8–15 feet). Again these exercises are performed in standing, with the feet positioned to challenge postural stability. The head is rotated as quickly as possible for 2 minutes, with the restriction that the visual target must remain in focus and stationary.

Gaze stability during head movements requires not only normal functioning of the VOR, but also interaction with other visual systems, such as the smooth pursuit system. To encourage this interaction, the x1 viewing exercise is modified. The individual is again challenged to maintain clear and stable vision during head movements; however, rather than use a stationary target, the individual holds the target and moves it in the direction opposite to the head movement (Fig. 28-3B). If the target moves at the same speed as the head but in the opposite direction, then the eyes have to move at twice the head velocity to maintain clear vision. Consequently this exercise is often referred to as times two (x2) viewing. This exercise can be performed in sitting, if necessary, and progressed to standing with a progressively decreasing base of support. The exercise can be performed with both a simple visual target as well as a target located in a complex visual background.

*Exercises to Foster the Substitution of Alternative Strategies for Gaze Stability* Bilateral vestibular hypofunction (BVH) may result in major or complete loss of bilateral vestibular function. Therefore, the exercises are designed to enhance the remaining function of the vestibular system and to foster substitution for the loss of vestibular function with alternative strategies to maintain gaze stability (66). In the absence of vestibular signals, these individuals must use cervical inputs and knowledge of upcoming head movements (pre-planning) to generate the compensatory eye movements (see Table 28-1).



**FIGURE 28-3**

Exercises to induce adaptation of the vestibulo-ocular reflex. (A) x1 viewing exercise. The patient views a stationary target, which should be a letter, number or word (in this case the letter A), while he turns his head back and forth. The speed of the rotation is increased to the point where faster movements would induce oscillopsia. Both horizontal and vertical rotations are performed. (B) x2 viewing exercise. The patient views a target that moves in the opposite direction of the head movement, while he turns his head back and forth. As with the x1 viewing exercise, the target should be a letter, number or word (in this case the letter A). The speed of the rotation is increased to the point where faster movements would induce oscillopsia. Both horizontal and vertical head rotations and target movements are performed

The cervical-ocular reflex (COR) normally contributes less than 15% to the generation of compensatory eye movements for low frequency head rotations (66). Following bilateral vestibular loss, the COR can account for up to 25% of the compensatory eye movements for both low and high frequency head rotations (68). The x1 viewing exercise described in the previous section can be used to increase the gain of the COR and to enhance the remaining function of the VOR. Generally, these exercises will be conducted at lower velocities than in individuals with unilateral vestibular hypofunction. When these exercises are performed actively, the CNS can also use foreknowledge of the upcoming movement to generate a compensatory eye movement. If performed passively, then the preplanning information is lost and the eye movements must be generated by the COR.

Another exercise which may improve the response of the COR, but also uses the central nervous system's

**TABLE 28-1**  
*Exercises to Promote Alternative Strategies for Gaze Stability*

1. X1 viewing exercises
2. Active eye-head movements between two targets:
 

Horizontal targets: Look directly at one target being sure that your head is also lined up with the target. Look at the other target with your eyes and then turn your head to the target. Be sure to keep the target in focus during the head movement. Repeat in the opposite direction.

Vary the speed of the head movement, but always keep the targets in focus.

*Note:* Place the two targets close enough together that when you are looking directly at one, you can see the other with your peripheral vision. Practice for 2–5 minutes, resting if necessary. This exercise can also be performed with two vertically placed targets.
3. Visualization of imaginary targets:
 

Look at a target directly in front of you. Close your eyes and turn your head slightly, imagining that you are still looking directly at the target. Open your eyes and check to see if you have been able to keep your eyes on the target. Repeat in the opposite direction. Be as accurate as possible.

Vary the speed and the amount (stopping point) of head rotation.

Practice for 2–5 minutes, resting if necessary.

*Note:* This exercise can be performed actively or passively while looking at a near target (within 2 feet) or at a distant target (across the room); it can also be performed vertically.

knowledge of upcoming movements, is the visualization of a remembered target location during head rotation. In this exercise the patient fixates a visual target, closes his eyes, and rotates his head in one direction. While turning his head, the patient attempts to keep his eyes on the target location. When the patient stops the head rotation, he opens his eyes and looks at the visual target. If his gaze is accurate, he will be looking directly at the target. If his compensatory eye movements are insufficient, his eyes will have moved with his head and he will have to make a corrective saccade to view the target. This exercise should be performed with both horizontal and vertical head movements. The visual target should be placed at different eccentric positions and different distances relative to the patient. The degree and speed of the rotation should be varied to force the patient to attend to all sensory cues.

Difficult tasks for individuals with BVH are gaze shifts that require both eye and head movements. Normally this task is accomplished by a patterned response. Initially, there is a saccade that is directed toward the object of interest. A head movement towards the target begins shortly after the saccade. While both the eye and head are moving towards the target, the VOR must be suppressed. When the eye reaches the desired location, the head is typically still turning. At this point the VOR must be used to keep the eyes on target during the remaining head movement. For patients with BVH, this head movement would cause the eyes to move beyond the intended object of interest and visual acuity would diminish. Individuals with BVH typically adopt one of two strategies to minimize this visual disturbance (68). One

strategy is to make a hypometric saccade and allow the head movement to carry the eyes onto the object of interest. A second approach is to make an accurate initial saccade, followed by a corrective backward saccade that is triggered by the head movement. Both of these strategies will minimize the amount of time that the visual image is not on the fovea. We do not attempt to teach one strategy or the other. We simply have the patient perform an activity that will encourage adoption of one of these strategies. For instance, two targets are placed at eye level, arm's length away, and slightly greater than shoulder width apart. The patient starts with her head rotated to the right, directly facing the target. The patient then shifts her gaze to the target on the left. The patient is told to move both her head and her eyes so that she is looking directly at the target. She is instructed to perform this as quickly as possible, but to keep the target in focus. The movement is then repeated in the opposite direction.

### **Treatment of Motion Sensitivity**

Symptom provocation due to either head movements or visual motion is a common finding in individuals with vestibular dysfunction, and these findings are very common in individuals with dizziness secondary to TBI. Patients with sensitivity to head movements will describe increased symptoms associated with either head movements in general or rather specific movements. Patients with visual motion sensitivity will note increased symptoms when they are in busy visual environments such as crowds, department / grocery stores, or in traffic. The determination of head motion or visual motion sensitivity can often be made through the



patient interview. One method of determining head motion sensitivity is through a series of rapid positioning maneuvers designed to elicit symptoms (69). These movements incorporate horizontal, vertical, and diagonal head movements with the head in different orientations relative to gravity. The symptom severity and duration in each of these movements is noted and used to determine a “Motion Sensitivity Quotient”. The results of this test can be used to identify patterns of motion that provoke symptoms and to track changes in the patient’s motion sensitivity. The general approach to the treatment of motion sensitivity is that of habituation, defined here as the long-term reduction of the response to a noxious stimulus (specific movement), brought about by repeated exposure to the provocative stimulus. The motion-provoked symptoms in patients with vestibular dysfunction is thought to be due to the sensory mismatch among the vestibular, visual, and somatosensory systems, which is brought about by movement. Repeated exposure to these movements is thought to lead to central adaptation and reorganization of the inputs to decrease the sensory mismatch and decrease the symptoms (70).

*Exercises to Decrease Head Motion Sensitivity* The x1 viewing exercises, since they involve head movements can be used as a habituation exercise. So in some individuals with head motion sensitivity, who have normal visual acuity during head movements, performance of the x1 viewing exercise can lead to a reduction in their symptoms. For other individuals, however, performing the x1 viewing exercise may be too symptom provoking, or may not reduce all of their symptoms. In these cases habituation exercises may be used to reduce the motion sensitivity. These exercises are generally of greater amplitude and velocity than the x1 viewing exercises. However, the amplitude and velocity of the head movement is adjusted

to the patient’s condition. The exercises are designed to provoke symptoms, but following completion of the each exercise session, the symptoms should return to baseline levels within 15 to 30 minutes. The selection of the exercises and movement patterns may be based on either the patient’s description of provocative movements or on the results of the motion sensitivity examination. Examples of these exercises are presented in Table 28-2. Typically up to 4 specific movements are selected for each exercise session. Generally, one pattern of movement (horizontal, vertical, or diagonal) is chosen for the exercise program and then the program progressed over time. Caution should be taken with the exercises that have patients move from a “heart low” to “heart high” position if there are concerns about orthostatic hypotension.

*Exercises to Decrease Visual Motion Sensitivity* A number of the previously described exercises can be used to try and decrease visual motion sensitivity. Performance of the x1 viewing exercise with the visual target located in front of a complex visual background can be used as an effective exercise to decrease visual motion sensitivity. As noted above, this exercise will induce movement of the visual background in an anti-compensatory fashion relative to the head movement. The habituation exercises described above (particularly the horizontal and vertical head movement exercises), if performed with eyes open, facing a visual scene with lots of color and contrast, can also be used as an exercise to decrease the visual motion sensitivity. If the combination of visual motion and head motion is too symptom provoking, then another exercise, which does not involve head movement, may be used. In this case, the patient performs a visual following task, with the object of interest located in front of a busy visual background. The exercise is similar to the x1 viewing

**TABLE 28-2**  
*Exercises to Decrease Motion Sensitivity*

1. While sitting, turn your head quickly from right to left 5 times. Look in the direction you are turning. Wait for your symptoms to subside. Repeat 3 times.
2. While sitting, alternate looking up at the ceiling and down at the floor quickly 5 times. Look in the direction you are moving your head. Wait for your symptoms to subside. Repeat 3 times.
3. Sit on the edge of your bed. Turn your head about 45 degrees to the left. Now quickly lie on your right side. Wait for any symptoms to pass. Keeping your head turned, quickly sit up. Again, wait for the symptoms to pass. Now turn your head approx. 45 degrees to the right. Quickly lie on your left side. Wait for the symptoms to pass. Quickly sit upright. Wait for the symptoms to pass. Repeat 5 times.
4. Lie on your back. Quickly roll to the right side. Wait for symptoms to pass. Return to your back. Quickly roll to the left side. Wait for symptoms to pass. Return to your back. Repeat 5 times.
5. While sitting in a chair, bend your head forward about halfway toward your knees. Now quickly sit upright. Wait for the symptoms to pass. Repeat 5 times. (*Note:* this can be done tipping the head to right or left knee instead of straight down if that movement is more provocative)
6. Stand in a corner with your back to the wall. Now make a quick turn so that you are facing the wall. Stop and wait for symptoms to pass. Now make a turn in the opposite direction so that your back is again facing the wall. Repeat 5 times.

exercise; however, the patient keeps their head still and moves the visual target from side to side (or up and down). Since the smooth pursuit system is limited in frequency and velocity, the movement of the target will be relatively slow. Again, the patient's task is to keep the visual target in focus during the movement. Like the x1 viewing exercise, this exercise is performed for 2 minutes at a time.

Another approach to this problem is to immerse patients in the environments that provoke their symptoms. Patients are encouraged to walk through grocery stores, department stores, shopping malls, or crowds (provided these environments provoke symptoms). They can grade the intensity of the exercise in several ways. One, they can control their exposure by limiting the time they are in the particular environment. They can often adjust the intensity of the visual motion by selecting different times of the day to perform this exercise. Early in the morning there are generally fewer people in the stores than later in the day or evening. As their symptoms decrease, they are encouraged to walk for longer periods of time and at times when the stores are more crowded.

### **Treatment of Postural Instability**

Another function of the vestibular system is to help maintain postural stability, or postural control. Postural control is defined as the ability to maintain the center of gravity over the base of support within a given sensory environment. Postural control requires the ability to perceive sensory information (somatosensory, visual, and vestibular), to centrally weight and select the appropriate sensory information, and to generate a suitable motor response to maintain stability. The selection of the appropriate motor response is based upon the available sensory information, biomechanical constraints, environmental contexts, and prior experience. Vestibular, visual, and somatosensory cues are all used to detect movement of the body and to trigger appropriate postural responses. If the vestibular system is not functioning appropriately, then the individual will have difficulty maintaining their balance when visual or somatosensory cues are altered or absent (e.g. at night, walking on uneven or compliant surfaces). In individuals with remaining vestibular function (for example those with a unilateral vestibular deficit), the exercises are designed to foster adaptation of the remaining vestibular signals to generate the appropriate postural responses. Unlike the VOR, the signal utilized for modification of the vestibulo-spinal reflexes (VSR) is not known. Presumably a similar visual-somatosensory-vestibular error signal is needed (71). Exercises used in the treatment of UVH are designed to generate these error signals and thereby foster adaptation of the vestibular system (66). For those individuals without vestibular function (for example those with bilateral vestibular loss) there is no remaining

vestibular signal to adapt. Consequently, the exercises for these individuals are designed to promote the use of alternative strategies to promote postural stability. The two general exercise approaches and the rationale behind the exercises will be explained separately.

*Exercises to Improve Static and Dynamic Postural Stability in Patients with Remaining Vestibular Function* Exercises to promote static and dynamic postural stability in various sensory environments involve the manipulation of visual, vestibular and somatosensory cues to force the individual to utilize vestibular cues for postural stability (see Table 28-3). Single, progressing to multiple, sensory modalities are manipulated to increase the difficulty of the postural control task. Varied sensory conditions may include: 1) somatosensory changes (firm, conforming, level, uneven, and moving surfaces), 2) visual changes (eyes open with foveal, full field, or moving visual stimuli, or eyes closed), and 3) vestibular changes (different head orientations and head rotation). The exercises are also progressed from static to dynamic activities.

The initial exercise to improve standing balance progresses from standing with minimal external support to standing without assistance. Once the individual can stand independently (usually within 2 to 3 days from the onset of the UVH), they perform the exercise with a decreasing base of support to increase the task difficulty. This exercise sequence may be performed with the arms outstretched to facilitate stability. As the individual's balance improves, the exercise is performed with the arms at the side or folded across the chest to increase the difficulty of the task. Sensory cues can be modified to increase the difficulty of the task. Visual cues for postural stability can be removed by having the individual perform the exercise with their eyes closed. Having the individual stand on 4-inch thick, medium density foam, or pillows while assuming the various stance positions can alter somatosensory cues. Obviously, visual and somatosensory can be altered simultaneously by having the individual perform the exercise with eyes closed while standing on the compliant surface. This sequence of standing balance exercises can be repeated while standing on inclines. The exercises can also be repeated with the head tilted in various directions to alter the otolith inputs.

Exercises for improving dynamic postural stability involve progressively more difficult head and trunk movements while moving through space. Initially, the individual works on simple weight shifting activities, holding the end range position for three to five seconds, and independent ambulation. The progression from assisted to independent ambulation is usually very rapid. Providing there are no underlying orthopedic or other neurological problems, the patients are generally able to walk independently within several days of the initiation of ambulation. Typically these individuals avoid head rotation

**TABLE 28-3**  
***Exercises to Improve Static and Dynamic Postural Stability***

The purpose of these exercises is to develop strategies for performing daily activities even when deprived of visual, somatosensory, or normal vestibular inputs. The activities are designed to help you develop confidence and establish functional limits. On all of these exercises, precautions should be taken to prevent *falls*.

1. Stand with your feet shoulder width apart with both hands helping you keep your balance by touching a wall (or countertop). Take your hands off the wall for longer & longer periods of time while keeping your balance. Try moving your feet closer together. Practice for 5 minutes.
2. Stand with your feet shoulder-width apart, eyes open, looking straight ahead at a target on the wall. Progressively narrow your base of support (move your feet one inch at a time) from feet apart, to feet together, to a semi-heel-to-toe position, to heel-to-toe (one foot in front of the other), to heel-to-toe onto to on "tip-toes."  
Do the exercises first with arms outstretched, then with arms close to your body, and then with arms folded across your chest.  
Hold each position for 15 seconds, and then move to the next most difficult position.
3. Repeat exercise #2 with head bent forward 30 degrees and then bent back 30 degrees.
4. Repeat exercise #2 with eyes closed, at first intermittently and then continuously, while making an effort to mentally visualize your surroundings.
5. Repeat exercise #2 and/or #4 while standing on a foam pillow.
6. Stand with your feet a comfortable distance apart and eyes open. Now sway forward and back so that weight shifts from your toes to your heels. Make sure there is no jack-knifing at the hips. Practice this for a minute or so. Now stop and close your eyes and stand as still and steady as possible. To progress this activity: Practice the swaying activity with eyes closed, practice with narrow base of support, and practice on compliant surfaces.
7. Walk close to a wall with your hand available for balancing. Walk with a narrower base of support. Finally, walk heel-to-toe. Do this with eyes open / closed. Practice for 2 minutes.
8. Walk close to a wall and turn your head to the right and left as you walk. Try to focus on different objects as you walk. Gradually turn your head further & faster. Practice for 2 minutes.
9. Practice turning around while you walk. At first, turn in a large circle but gradually make smaller and smaller turns. Be sure to turn in both directions.
10. Take 5 steps and turn around to the right (180°) and keep walking. Take 5 more steps, turn left (180°) and keep walking. Repeat 5 times, rest, and repeat the entire sequence.
11. Walk outside on an uneven surface or walk inside on a compliant surface.
12. Climb up your stairs without using your arms. Practice for 2 minutes.
13. Practice walking in a grocery store. To make it more difficult:
  - try to walk without a grocery cart,
  - go when there are few people there, then when it is crowded,
  - increase the number of aisles you walk through.
14. Practice walking in a shopping mall:
  - first when it is not crowded, then
  - when it is crowded, but walk with the flow of the crowd, then when it is
  - crowded, but walk against the flow of the crowd.
15. Participate in golf, tennis, dance, racquetball, etc.

*The following balance exercises are performed at home with a partner:*

While standing, kick a ball between you.

Practice batting a nerf ball.

Play a game of catch. Progress in the following manner:

Start with just an easy game keeping the ball in the midline.

Then throw to either side.

Take a step to the side to catch the ball. Your partner should let you know to which side he will be throwing the ball.

To further progress throw randomly from one side to another.

Catch the ball without taking a step as the ball is thrown to either side.

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*All of the activities listed above can be performed on a compliant surface.*

during ambulation and assume a wide base of support while walking. Once they are able to walk independently, low frequency, small amplitude head rotations with concurrent gaze shifts are incorporated into the exercise program. To avoid excessive symptom provocation and marked gait ataxia, the individual performs the head rotation – gaze shift every 5th step. This may be performed with both horizontal and vertical head movements. This exercise forces the individual to adapt to the head rotations and prevents them from using visual fixation for postural stability. As recovery proceeds, the amplitude and peak velocity of the head rotation can be increased. To decrease the base of support, the patients walk with a progressively narrower base of support, ultimately walking heel to toe (tandem gait). Patients can also walk with the head tilted in either the frontal or sagittal planes to alter the otolith inputs. Patients are also encouraged to walk outdoors, which poses two distinct sensorimotor challenges. One, the support surface will change, which necessitates rapid postural adjustments. Two, visual cues for postural stability are at a greater distance than those indoors. This change in visual cues often causes increased dysequilibrium because the normal degree of postural sway results in smaller movements of visual images across the retina. This is an analogous situation to the normal experience of height vertigo.

The exercises described above challenge an individual's ability to move linearly. Another set of exercises is designed to rehabilitate the ability to rotate. This exercise involves walking approximately ten feet and turning around 180°. This is then repeated with rotation in the opposite direction. As the individual's balance improves, the radius of the turn is gradually decreased. This exercise can ultimately be performed with an abrupt rotation, or standing pivot. This exercise can also be performed with the eyes closed. A further extension of the exercise for the advanced stages of the rehabilitation process is rapid rotation combined with higher velocity linear movements. Examples include dance steps or shifting from a forehand to backhand in any of the racquet sports.

A more rigorous exercise to improve dynamic postural stability is hopping on one foot. Caution must be used with this exercise, or any exercise, which involves jarring movements to the head, post-surgery. There must be adequate time to allow for healing of the involved tissues before these strenuous exercises can be attempted. The difficulty of this exercise can be increased by eye closure. One of the final exercises used in the rehabilitation of dynamic postural stability is an obstacle course, where the individual walks over various surfaces, rotates, side-steps, and goes through a series of position changes (sit to stand, bending over, reaching, etc.). Lastly individuals are encouraged to resume their normal activities, especially those activities that involve postural changes and head movements, such as dancing, racquet sports, and golf.

*Exercises to Improve Static and Dynamic Postural Stability in Patients without Vestibular Function* The exercises to improve static and dynamic postural stability are similar to the exercises described for patients with remaining vestibular function (Table 28-2). Unlike the individuals with compensated unilateral vestibular lesions, those with bilateral vestibular hypofunction will have varying degrees of difficulty maintaining their balance when both visual and somatosensory cues are perturbed. Consequently, the exercises may need to be modified to allow the utilization of one sensory cue or to decrease the task complexity by widening the base of support.

The initial postural stability exercises for patients with BVH are simple standing balance exercises, with the goal of developing independent stance. As the patient is able to stand without assistance, the exercise is made more challenging by progressively decreasing the base of support, until balance cannot be maintained. As with the static postural stability exercises for individuals with UVH, these exercises can be performed initially with the arms outstretched, then at the side, and finally folded across the chest. In these exercises both visual and somatosensory cues are available to the patient.

Individuals with BVH tend to initially rely solely on visual cues but gradually utilize somatosensory cues for postural stability (72). If the examination of the patient reveals that they are not using somatosensory cues for postural stability, then the standing balance exercises can be performed with the eyes closed. Eye closure may need to be intermittent at first but is progressed until the patient can perform the exercise for 30 seconds. It is often helpful in the beginning stages of this exercise to have the individuals visualize their surroundings when their eyes are closed. In addition, active weight shifting with eyes closed increases somatosensory awareness and awareness of the supporting surface. Should the unlikely situation arise where an individual is attending to somatosensory and not visual cues, the postural stability exercises can be performed with eyes open while standing on a compliant surface, such as a foam pad, to perturb the somatosensory inputs. Altering visual and somatosensory input to optimally challenge the individual should only be performed with the necessary safety measures to prevent falls.

The role of cervical input in the maintenance of postural stability is questionable. Bles et al (73). reported that static cervical positions did not contribute to postural stability in BVH. In light of these findings, the static postural exercises performed with head tilts may challenge the balance system by changing the visual frame of reference. The role of dynamic cervical input is not known at this time. Individuals with BVH have difficulty maintaining balance with head rotation during ambulation. This degradation of balance may be due to the loss of a stable visual frame of reference. However, their ability to walk and turn their head does improve with practice.

Patients with BVH also tend to walk with a wide base of support. Having these patients walk with a decreased step width, ultimately ambulating heel to toe, can challenge their dynamic postural stability. Changes in direction, as described for the patients with UVH, are also a challenge for the individual with BVH. An obstacle course or functional tasks that require positional changes, movement, and changing visual or somatosensory cues are also beneficial by forcing the patient to adapt to changing environmental conditions and to shift between the available sensory cues.

Patients should be instructed in behavioral and environmental modifications to optimize function and reduce the risk of falling. Environmental modifications may include: adequate lighting (including emergency lighting in case of a power failure), removal of thick carpeting and area (or throw) rugs, non-skid floors, pathways clear of obstructions, stable tables and chairs, reorganization of cabinets and shelves to minimize bending and reaching, and stairs with railings. Behavioral modifications may include: learning to plan movements, avoiding hurried movements, sitting to work, visual fixation on distant objects for stability, light touch on objects for balance, restricting rapid head movements and walking in crowds. Frequently, individuals with BVH are unable to drive due to oscillopsia. For those that have adequate visual acuity during head movements, many are unable to drive at night due to reduced visual cues. While assistive devices may not be needed around the home or during the day, the devices may be needed for safety concerns at night, in unfamiliar environments, and on uneven surfaces. For some individuals, an assistive device is necessary as an outward sign that there is a physical problem. Since there are no outward signs of a vestibular deficit, the individual is concerned that their staggering may be perceived as inebriation.

### **Exercise Guidelines for Individuals with TBI**

Confounding orthopaedic and neurological factors often complicates treatment of vestibular deficits in patients with traumatic brain injury. First, the exercise programs described above will provoke the patient's symptoms. The exercises, if conducted appropriately, will generate an error signal in the CNS, which is thought to provoke symptoms of vertigo, dizziness or dysequilibrium. Depending upon the individual's symptoms, cognitive level, and degree of agitation, the symptom provocation may not be tolerated well. In those individuals with marked dizziness, motion sensitivity and agitation, the x1 viewing exercises may simply provoke too many symptoms. In these cases, it is recommended that the initial course of vestibular rehabilitation be simple habituation exercises, performed to tolerance. Once the habituation exercises have decreased the motion sensitivity, then x1 viewing exercises, if needed, may be initiated.

As the patient's status improves and their agitation decreases, the intensity of the exercises (either habituation or adaptation exercises) can be increased. With this increase, patients are told to expect greater symptom provocation and that provocation of their symptoms is actually beneficial to their recovery. A general guideline is that symptoms may be provoked for 15 to 30 minutes following the exercises. If the increased symptoms persist longer, the speed, duration, or context of the stimulus should be reduced. If the exercises are performed in a manner that does not challenge the system or provoke the symptoms, then the error signal will not be generated. Consequently, there will be no stimulus for adaptation. Similarly, the use of CNS depressants (such as meclizine or benzodiazepines) to treat the symptoms of vertigo and dysequilibrium are thought to retard the adaptation process.

The exercises may need to be modified due to other aspects of their injury. If for example, the patient suffers diplopia on lateral gaze to one side due to lateral rectus muscle palsy from the injury, then the x1 viewing exercise is modified to avoid lateral gaze to the affected side. Similarly, static and dynamic postural stability exercises may need to be modified due to muscle weakness, spasticity, or lower extremity fractures. Clinical judgment is required to adapt the basic exercise programs described above to meet the needs of the individual patient.

### **Vestibular and Balance Rehabilitation Therapy Outcomes**

At this point, there have been no comprehensive studies examining vestibular and balance rehabilitation therapy outcomes inpatients with TBI. There are, however, numerous studies that have demonstrated the efficacy of VBRT programs in different populations of patients with vestibular disorders (54, 74, 75–77). Herdman and colleagues (74) demonstrated that, following acoustic neuroma resection, patients that underwent vestibular adaptation exercises demonstrated improvements in dysequilibrium, ataxia, and static postural stability as compared to individuals that had undergone a sham exercise program. Horak and colleagues (54) reported that individuals with chronic vestibular dysfunction treated with vestibular rehabilitation exercises developed improved motion sensitivity measures and static postural stability measures when compared to similar individuals treated with either condition exercises or vestibular suppressant medication. Similar results have been shown in patients with bilateral vestibular loss (76). Shepard and colleagues (75) reported that patients that underwent a customized VBRT program had greater improvements than those that received a generic VBRT program. Are the exercises always effective? No, but reports suggest that the exercise approach is successful in reducing symptoms and improving function up to 85% of the time (75, 78).

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# 29

## Evaluating and Treating Visual Dysfunction

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### INTRODUCTION

Complaints concerning vision are common following a traumatic brain injury (1). A traumatic brain injury can cause a wide variety of symptoms related to vision such as headaches, diplopia, vertigo, asthenopia, inability to focus, movement of print when reading, difficulty with tracking and fixations, and photophobia. Persons experiencing these types of visual problems frequently will have other medical sequela related to the TBI.

Epidemiological studies of vision problems relating to traumatic brain injury have been sparse in both literature and research. However, a limited number of studies demonstrate that vision dysfunction is common following a TBI and can affect any part of the visual process (2).

In one study, the most common complaint was blurred vision (46%) followed by diplopia (30%) and headaches (13%). Thirty-five percent of the subjects displayed a visual field defect of which the most common was a compression of peripheral fields followed by

homonymous hemianopsia. Thirty-three percent of the subjects experienced cranial nerve palsies of which third nerve palsy (exotropia) was the most common. Ninety-five percent of these subjects had normal funduscopic findings while of those with abnormal funduscopic evaluations, twenty-six percent demonstrated optic nerve abnormality.

Binocular dysfunction is highly prevalent (3) following a TBI and relate to many of the symptoms regarding vision that a person may experience (4). Often, exotropia (an eye deviated outward) or exophoria (tendency for the eyes to deviate) occur following a TBI either through direct cranial trauma or whiplash (5, 6).

Following a TBI, visual sensory deficits can be caused by areas other than the stria of the occipital lobe which is often noted as the primary visual cortex (7). The extent and impact of a TBI on overall sensory function can be quite profound but due to the true nature and primary influence of visual processing, no interference can be as significant as that of the visual system following a



TBI. Mechanisms for sensory deficits require awareness and recognition of the problem by the affected person without which, there is a significant potential for interference in the overall rehabilitation process (8).

The use of vision to lead and guide motor function is often compromised following a brain injury (9) affecting visual perception and visual motor dysfunctions. New evidence has emerged demonstrating that neuro-motor function also contributes to spatial awareness and affects egocentric concepts of visual midline (10) beyond the role of acuity. Visual midline is the perceived lateral and anterior-posterior visual concept of egocentric position relative to sensory-motor concepts. The influence of homonymous hemianopsia will also directly affect the perception of visual midline, posture, and balance.

Use of visual evoked potentials (VEPs) have disclosed that dysfunction in visual processing may be a cause of many of the conditions of strabismus following TBI (11). Researchers have also documented through VEP patterns that there are many visual abnormalities significantly related to the clinical disability of persons with TBI (12). The result of such research are leading many to begin questioning the traditional examination methods of examining persons with a TBI relative to diagnosing binocular dysfunction or to assess visual processing of the bimodal system of vision.

Recent studies (11, 13) involving visual evoked potentials (VEPs) have directed consideration that binocular dysfunction and visual midline shift are due to dysfunction of visual processing and not necessarily due to muscle or cranial nerve palsy following TBI. Until recently, research involving the bimodal process of vision had not been considered clinically relevant at the same level as binocular function. In particular, dysfunction of binocularity had been looked at primarily as the cause related to the symptoms. Understanding the true nature of the bimodal visual process may now give the documentation necessary to understand the nature of binocular function in relationship to cortical and subcortical mechanisms that organize vision and sensory motor information. In turn, the visual evoked potential may now give the researcher as well as the clinician the means to join in the study of process related to clinical function. In addition, it may also provide new means of understanding the significant interferences caused by TBI related to a wide variety of visual symptoms following a TBI.

It is common for persons to experience vertigo, dizziness, and other balance disorders following a TBI (14). While studies have emphasized the vestibular system as the primary mechanism for maintaining stability of the visual field, new information regarding the role of the pretectum and superior colliculus offers insight into vision stabilizing the retinal image and establishing peripheral fusion. In addition, the superior colliculus also mediates visual processing affecting posture, movement, and

orientation to positional space (15). A new model of processing related to the sensorimotor feedback loop providing a feedforward system to other higher areas of cortical function has been proposed and gives real insight into the role of the motor system affecting sensory perception and stability (16).

### VISION: A BIMODAL PROCESS

Seventy percent of all sensory processing in the entire body is directly affected by information coming from the two eyes (17). These visual influences are directed to the midbrain and the majority extend themselves to the occipital cortex for purposes of seeing (15). As a dominant system in the sighted person, vision is often taken for granted. Fortunately, we do not have to think about the process of using vision as we automatically employ vision in our daily activities. The important dynamics of visual processing are masked behind our intense attention and concentration to the accomplishment of the task at hand. For example, the task of writing involves vision but we do not think about where we are looking when we move the pen on the page. Nor do we think of how we see print as we read. Do we see each individual letter on the page or do we see more globally and embrace whole words and phrases?

Trevarthen (18) and Liebowitz and Post (19) have disclosed that there are two modes of visual processing; the focal process and the ambient process. The focal process delivers information for the purpose of attention, concentration, and higher cognitive processing. Information is sent primarily to the occipital cortex for the purpose of seeing detail. This is the portion of the system which enables us to attend to a task or concentrate. If we had only the focal process, the world we see would break apart into a mosaic of fragments. We would see only the lines, shadows, and shapes on a person's face and although we would see clearly, we would not be able to recognize the inter-relationship of all of these details. We would not be able to recognize the person's face as a familiar gestalt.

Approximately twenty percent of fibers from the peripheral retinas of both eyes are delivered to the midbrain (20). Here, the visual process matches information gathered from the kinesthetic, proprioceptive, tactile, and vestibular systems. This function has been labeled the sensory-motor feedback loop (21). It serves to organize spatial information about balance, movement, and orientation in space. The visual process is very much involved in movement and postural control. The superior colliculus, a critical area in the midbrain system, receives fibers from the optic tract via the superior brachium, occipital cortex via the optic radiations through the lateral geniculate, and from the spinotectal tract connecting it with

sensory motor information from the spinal cord and medulla. It is in the midbrain that sensorimotor matching concepts of midline, body awareness, posture, and orientation are established. Once this is accomplished, a feedforward phenomenon occurs. Information is relayed from the midbrain to the occipital cortex where it is used to preprogram the higher seeing area as to how to organize or look at incoming visual information. This is first done spatially and has been termed the ambient visual process. Following this, focalization on detail will occur. In this manner, the occipital cortex will organize information spatially before it looks at the detail. In other words, it is as if we know where to look before we completely identify the target. Spatial information from this midbrain ambient visual system is also used in other processing levels at the occipital cortex for purposes of bringing together detail information relative to spatial boundaries. In particular, the binocular coordination cells that receive information imaging from both the right and left eye have the primary purpose of beginning to integrate or fuse the two separate images together as one. It is the spatial information from the ambient visual process delivered by the superior colliculus that becomes the binding format of the fusion process (22).

In fetal development, the eye is created from endoderm, mesoderm, and neuroectoderm. Of importance is the fact that neuroectoderm also develops the cortex which allows for recognition that the eyeball is neurologically an end result in part of developing brain tissue. The eyeball is richly endowed with nerve fibers that feed all aspects of the cortex as well as relaying information to midbrain structures. Nerve fibers emanating from the macula or central portion of the eye will align centrally in the optic nerve and optic tract directing themselves to localize in central areas of the visual occipital cortex. Peripheral retinal nerve fibers orient themselves in the optic nerve and optic tract around the central fibers and align themselves in peripheral areas of the occipital cortex.

While the central image from the macula occupies the major portion of our cortical attention and concentration for perception and cognitive processing, how we organize and process visual information is not a simple phenomenon. The dorsal ganglion of the lateral geniculate body seems to function as an integrating center in addition to its role as a relay and distribution center. Therefore the lateral geniculate is important to the relay of visual information to portions of the brain other than the occipital cortex.

It has also been demonstrated that 20% of the peripheral retinal nerve fibers relay information through axons to the thalamus or midbrain for spatial match with kinesthetic, proprioceptive, and vestibular information being received from other sensory-motor systems. The developmental purpose is to organize spatial information to orient higher sensorimotor experiences affecting

posture, movement, and balance. Once this has been established, information from the thalamus is sent to higher cortical functions (16). The occipital cortex is not an exception to this process. It receives spatial information in order to organize the detail information processed.

Ganglion cells from the retina emanate through the optic chiasm to the optic tract where they reach three major destinations: 1) the lateral geniculate body for relay to the visual cortex, 2) the pretectal nucleus (pupillary constriction), and 3) the superior colliculus which becomes related to posture, movement, and orientation to positional space (15).

In order to shift the position of the eyes from one point to another, we must spatially orient to the next destination before shifting the eyes (aiming the fovea) to look at detail (23). The ambient process is critical for anticipating change. Without this process, visual information becomes isolated details and there is difficulty shifting visual regard and attention. Also, there is a lack of awareness of body position in a spatial context caused by a shift in visual midline. Due to a mismatch between the ambient visual process, the kinesthetic, proprioceptive, the vestibular input system and the ambient visual process, the concept of visual midline will shift. As will be discussed later in this chapter, if the visual midline shifts, it will reinforce and/or cause postural imbalances.

The ambient process is not a conscious process as is the focal system. We orient this portion of the visual system to monitor and manipulate the spatial environment. The ambient visual process works to integrate sensory-motor information. Without the ambient visual process, an individual would experience fragmented vision as well as difficulty with organizing posture and movement. The bimodal process, however, in many ways has been ignored and/or misunderstood clinically (24).

Ganglion cells traveling from the retinas can be categorized based both on physiology and function into three types; P-cells (parvocellular), M-cells (magnocellular), and K-cells (koniocellular). These cells provide information similar to that which was discussed previously regarding the focal and ambient process. The M-cells and P-cells provide a physiological substrate for the ambient and focal processes. M-cells transmit visual information about shape and movement rapidly, but without detail. P-cells transmit the detail information contained in shapes and are much slower. These cells emanate from the retina through two major brain pathways; the retino-geniculo-cortical pathway and the retino-tectal pathway. The retino-geniculo-cortical pathway contains both P-cells and M-cells and is the most recent in evolution providing a mechanism for focal processing in the cortex. The retino-tectal pathway is mainly derived from M-cells and is more primitive and provides a basis for spatial information particularly related to spatial orientation prior to focalization. For example, a saccadic eye movement (via the

ambient pathway) first requires spatial orientation to establish the direction and trajectory of the eye movement prior to the focalization response. The retino-tectal pathway is most critical in early development of the child and some functions are taken over later in development by the retino-geniculo-cortical pathway (25). However, the midbrain ambient system remains important for spatial orientation and balance. It can be demonstrated clinically that children and adults with oculomotor dysfunction and aspects of dyslexia affecting reading ability demonstrate improvement with pursuit tracking and saccadic fixations as well as with the ability to track a line of print with sensory motor support such as by physically pointing at words.

The P-cell subsystem has been related to the focal visual process whereas the retino-tectal projection of the M-cell subsystem is a substrate for the ambient visual process. Neurons in the retino-tectal pathway are almost completely myelinated at birth whereas those of the retino-geniculo-cortical pathway are not. It is also of interest to know that the superior colliculus has essentially a normal adult organization and neuronal activity at birth whereas the occipital cortex does not (26). These authors have emphasized that while cerebral cortical processes have taken over much of the visual motor functioning, massive innervations still remain between cortical and midbrain structures.

Through development, experience is established to couple and bring balance between the ambient and focal visual process as well as the M-cell and P-cell subsystems. While balance between the spatial (ambient) and detail (focal) visual processing systems provide a means by which organization of time and space become a normal process for humans, injury as a result of a TBI can affect the balance between the systems. A decoupling of the focal and ambient visual process including the magnoparvo cellular systems is suggested as a basis for interference with function and performance. M-cells have larger diameter axons and have demonstrated to be more susceptible to damage in conditions such as ischemia and glaucoma.

More specifically, the decoupling of cerebral blood flow (CBF) and cerebral glucose metabolism (CMGL) has been described. This decoupling is described in terms of ischemia-hyperemia resulting in metabolic imbalances which derange neuronal energy production and cell membrane permeability ultimately causing potential cytotoxicity (27) even in a minor whiplash accident. This can be the basis of visual problems following TBI.

A patient with mild TBI is most frequently underdiagnosed or misdiagnosed relative to visual impairments (28, 29). The walking wounded with a negative CT scan or MRI is a potentially classic case of an injured person whose symptoms are frequently dismissed as exaggerated and/or psychosomatic in origin. The many individuals

who suffer significant visual symptoms following a brain injury potentially suffer equally from discrimination without identification of the causative factors (29).

The basis of the dysfunction of the visual process is related to the traumatic force imposed upon the central nervous system whether through blunt trauma or inertial acceleration or angular acceleration trauma of whiplash (hyperextension/hyperflexion). This can affect potassium adflux and secondary calcium influx. It is the influx of calcium ions that activate cellular protease enzymes triggering cytoskeletal disruption and simultaneous neurotransmitter hypercholinergic activity.

It is hypothesized to be the cytotoxic response that initiates cytoskeletal collapse and ultimately deafferentation that is etiologic to the symptoms of post-trauma vision syndrome. In turn, the lifelong established engrams that provided the automaticity of controls affecting the very complex sensory motor components that subserve the visual process become eroded resulting in degradation of our dominant sensory perception, our dominant guidance system: visual information processing (30).

### POST-TRAUMA VISION SYNDROME (PTVS)

Following a TBI, visual symptoms may occur (31) such as diplopia, seeing words and print appearing to move, difficulty shifting gaze, difficulty adapting to environments where there is movement in the periphery (such as in a store), and photophobia (Table 29-1). Characteristically, an examination of the visual system may demonstrate binocular dysfunction such as strabismus, convergence insufficiency, divergence excess, oculomotor dysfunction, and accommodative insufficiency. Some researchers have reported that diplopia, reduced acuities, and poor accommodation are prevalent among those with traumatic brain injuries (28). Others have reported intermittent diplopia present in certain positions of gaze (31). Soden and Cohen (32) as well as Nelson and Benabib (21) have correlated postural adaptation of the body with compensation for vision dysfunction and diplopia produced in certain positions of gaze. In addition, these researchers have found secondary contracture and/or muscle spasms due to poor body posture. A high prevalence of exotropia and exophoria have been reported for persons who have suffered even a mild traumatic brain injury (4, 5, 33).

Studies of binocularity have recognized dysfunction of oculomotor, convergence, and accommodations. A high prevalence of exotropia (5, 6, 34) is evidenced in the literature. While symptoms and characteristics are logically related to the visual dysfunction attributed to nerve palsy (35), the mechanism for the cause of the binocular dysfunctions appear to be more complexly related to the affect of the trauma on the bimodal visual processing systems as related by more recent studies

**TABLE 29-1**  
**Post-Trauma Vision Syndrome**

Common characteristics and symptoms associated with post-trauma vision syndrome characteristics:

- Exotropia or high exotropia
- Accommodative dysfunction
- Convergence insufficiency
- Low blink rate
- Spatial disorientation
- Poor fixations and pursuits
- Unstable ambient vision

Symptoms:

- Possible diplopia
- Objects appear to move
- Poor concentration and attention
- Staring behavior
- Poor visual memory
- Photophobia (glare sensitivity)
- Asthenopic symptoms
- Associated neuro-motor difficulties
  - Balance and coordination
  - Posture

on visual evoked potentials (11, 13). In this study, the researchers demonstrated that changes in amplitude under binocular testing were found to correlate statistically with an experimental population (persons with TBI) compared to a control group of which the experimental group of subjects also experienced symptoms and demonstrated characteristics as discussed in the previous paragraph. An increase in amplitudes was produced following treatment with base-in prism and binasal occlusion for the experimental group of subjects. A decrease in amplitudes was found for those in the control group. Changes were also reported in amplitudes and latencies following a TBI.

The researchers have explained that following a TBI, there appears to be interference in the ambient (spatial) organization of the visual field which as a result, affects the focalization process (36). As mentioned previously in this chapter, the spatial match of information between the ambient and sensory motor process can provide a feedforward (37) to the higher cortical processes including the occipital cortex of which the binocular integration cells require the spatial information to bind and establish peripheral vision fusion. A decrease in amplitude of the binocular visual evoked potential as demonstrated by the study emphasizes the role of the ambient visual process in providing this spatial binding for the fusion process. In turn, the decrease in the amplitude provides evidence of the lack of ambient vision feedforward support for higher binocular fusion prior to the focal visual process establishing awareness of detail.

The result of the dysfunction of ambient visual processing becomes characteristic of the binocular dysfunctions such as convergence insufficiency, accommodative insufficiency, exophoria, and may even be the basis for post-traumatic exotropia (38).

The characteristics of dysfunction of the binocular vision process as well as commonly measured comitant and noncomitant strabismus may be more a function of disruption related to ambient and focal visual processing than of specific neuronal interferences. Other studies have demonstrated that lesions in the superior colliculus can produce disturbances of convergence ability (39).

The dysfunction and lack of support through ambient visual processing leaves the person compromised in the attempt to use the focal visual process which isolates detail and does not serve the need for anticipation of change (23). For example, following a TBI, persons will often have to work harder at near vision tasks. The research provides evidence that the ambient process being compromised also interferes with the anticipatory spatial role to provide for release of fixation and detail as well as for change. In turn, the visual process becomes focally bound, isolating to detail rather than utilizing the ambient visual process for release from detail and the anticipation of spatial organization that affects continuity and sequence of visual performance.

This research also demonstrates that the structure of binasal occluders (vertical boundaries in the nasal portion of the visual field) in addition to base-in prism (prism affecting spatial organization), rebalances the ambient visual process. In turn, a reduction in symptoms was noted in these subjects corresponding to implementation of this mode of treatment. Specifically, subjects reported a significant reduction in symptoms (11) as previously mentioned.

The effects of dysfunction between ambient and focal processing as related to common characteristics of binocular dysfunction as frequently seen following a TBI are more common than previously recognized. Binocular dysfunction such as convergence insufficiency is a frequently misdiagnosed condition following a traumatic brain injury. Convergence insufficiency should always be considered in the diagnosis of patients with head trauma.

The dysfunction relative to focal and ambient visual processing has been termed post-trauma vision syndrome (PTVS). Persons who suffer from post-trauma vision syndrome will often have clear sight and their eyes will be healthy. Upon being referred for a routine eye examination, if the examiner is not familiar with PTVS, the examiner will often report that there is nothing wrong with the person's eyes and the symptoms appear to be more psychological in nature. Many persons will spend years suffering from this condition unless it is diagnosed and treated appropriately. Needless to say, this can be the cause of additional inappropriate referral and treatment

at a high cost to families and third party reimbursement systems. Appropriate treatment will not only reduce symptoms, but directly affect attention, concentration, and cognitive processing while preventing secondary emotional complications. The methods of evaluation and treatment through neuro-optometric rehabilitation and neuro-ophthalmological evaluation will be discussed later in this chapter.

### **VISUAL MIDLINE SHIFT SYNDROME (VMSS)**

Postural orientation is vital for daily function for both adults and children. Postural adaptation that begins in the early stages of development provides a means for the infant to organize space for balance, spatial orientation, and ambulation. For functioning adults and children, anti-gravity alignments are initiated with limbs and/or with head movements. The vestibular system contributes a balance response necessary when the center of gravity has shifted while the cerebellar and midbrain structures through ambient/sensory motor support contribute to the desired qualities of smoothness and coordination for motor planning.

The ambient visual process is primary in the establishment of postural orientation related to boundaries by orienting boundaries in the vertical and horizontal planes with spatial information from sensory motor systems. Early in development, this establishes concepts of visual midline that provide experience for postural orientation (20). Established in relationship with multi-sensory motor cooperation, the ambient visual process together with sensory motor match, feedforwards information to diverse areas of the cerebral cortex including the occipital cortex. This vital component enables anticipation for postural adaptation and movement (37).

Following a TBI, a person may be left with hemiplegia or hemiparesis. The loss of neurological and motor function has traditionally been thought to be the sole cause for the inability to weight-bear on the affected side. Also, in cases of visual field loss such as with homonymous hemianopsia, it has been observed that individuals will begin to lean away from the side of visual field loss even if they do not have a hemiparesis.

Prior to the consideration of vision as a bimodal process, discussion has been centered on a lack of visual cognition and attention leading to neglect (40, 41). These authors have identified the phenomenon where people have limited or no attention to a specific side of their body as well as correlating field of vision. Right hemisphere damage often produces the characteristic left field neglect (42, 43). The spatial component of vision has been primarily considered related to the relationship of magnocellular function with right hemisphere involvement. The complete concept of the ambient process related to

midbrain and sensory-motor interaction should also be considered.

Relative to the concept of the bimodal process of vision, inattention is a focal processing phenomenon. The authors of this chapter offer the possibility that the focal visual processing dysfunction of inattention is secondary to the spatial ambient visual processing disorder that is more directly associated with the affect on sensory-motor processing from the TBI.

Studies (10) have demonstrated that the visual midline will shift relative to a hemiparesis and/or homonymous hemianopsia. This may be observed by passing an object in front of a person's face and asking them to report when the object appears to be directly in front of their nose. In the case of a visual field loss such as a homonymous hemianopsia, the person will often report the target in front of their nose when it is directed to the side away from the visual field loss. An interesting observation occurs when working with patients with hemiparesis or hemiplegia. The person will also project the concept of midline in the majority of cases by leaning away from the neurologically affected side. The shift affects weight-bearing on the affected side in most cases and in turn, interferes with aspects of physical rehabilitation. The shifting of perceived visual midline away from the affected side is a compensatory mechanism and essentially reinforces the neglect of visual space caused by the hemiparesis and/or hemianopsia.

The shifting of the visual midline is caused by a distortion (compression and expansion) of the ambient visual process. The midline can shift laterally and/or in the anterior/posterior axis. The perceived visual midline will usually shift away from the affected side. This has been termed visual midline shift syndrome.

### **NEURO-OPHTHALMOLOGY**

Progress and overall rehabilitation for a person who has suffered a TBI are often interfered with due to visual problems that are sometimes ignored or misdiagnosed (2).

The provision of skilled neuro-ophthalmological services can positively affect the rehabilitation outcome. Referrals for neuro-ophthalmological evaluations are often initiated by physicians or rehabilitation professionals and optometrists practicing neuro-optometric rehabilitation who recognize visual interference with daily living skills and/or perceptual motor function.

The literature lacks good demographic studies on the prevalence of neuro-ophthalmological problems in TBI. Sabates reports that of 181 consecutive patients referred with visual complaints following head trauma, the most common etiology was motor vehicle accident in 57% of the cases. For direct trauma to the head, 15% were represented and 13% were related to injuries

sustained from a fall. He also reports that in over 88% of the eyes tested, acuity of 20/20 was reported. Of this population, 33% suffered cranial nerve palsy.

## NEURO-OPTOMETRIC REHABILITATION

Neuro-optometric rehabilitation represents a new and evolving specialty within the profession of optometry devoted to clinical assessment and rehabilitative treatment of visual binocular/processing disorders following a traumatic brain injury. While there is overlap in the assessment between ophthalmological/neuro-ophthalmological and neuro-optometric rehabilitation, the latter emphasizes rehabilitation of visual processing disorders. The fields of ophthalmology and optometry work in conjunction with individuals who have suffered visual and ocular-visual problems following a TBI.

Neuro-optometric rehabilitation is defined as:

Neuro-optometric rehabilitation is an individualized treatment regimen for patients with visual deficits as a direct result of physical disabilities, traumatic and/or acquired brain injuries. Neuro-optometric therapy is a process for the rehabilitation of visual/perceptual/motor disorders. It includes but is not limited to acquired strabismus, diplopia, binocular dysfunction, convergence, and/or accommodation, paresis/paralysis, oculomotor dysfunction, visual spatial dysfunction, visual perceptual and cognitive deficits, and traumatic visual acuity loss.

Patients of all ages who experience neurological insults can benefit from neuro-optometric rehabilitation. Visual problems caused by traumatic brain injury, cerebrovascular accident, cerebral palsy, multiple sclerosis, etc. may interfere with performance causing the person to be identified as learning disabled or as having attention deficit disorder.

The visual dysfunctions can manifest themselves as psychological sequela such as anxiety and panic disorders as well as spatial dysfunctions affecting balance and posture. A neuro-optometric treatment plan improves specific acquired vision dysfunction determined by standard diagnostic criteria. Treatment regimens encompass medially necessary noncompensatory lenses and prisms with and without occlusion and other appropriate rehabilitation strategies (23).

The role of the ophthalmologist is to provide excellence of care relative to treatment of disease and trauma affecting the eye orbit and neurology affecting visual function. The ophthalmologist can and should be involved in treatment for acute care as well as long term ophthalmological needs for the person who has suffered a TBI.

The optometrist practicing neuro-optometric rehabilitation can affect visual processing disorders such as PTVS, VMSS, and other binocular spatial disorders

causing diplopia, vertigo, etc. as rehabilitation is established. The neuro-optometric rehabilitation assessment includes a careful review of medical and rehabilitative records as well as establishing a history based on visual and spatial dysfunction.

## Evaluation and History

The neuro-ophthalmological and neuro-optometric rehabilitation assessment requires a complete history and differentiation of symptoms and characteristics from pre-morbid conditions. The symptoms must be assessed relative to the medical history and a complete review of medical records and medications is imperative. It is important to reconstruct the event relative to the history in order to assess injury and lesions relative to inertial force and impact. Understanding the pre-event medical history is necessary relative to determining the nature of injuries.

*Oculomotor and Binocular Function Assessment* An oculomotor evaluation is performed to determine cranial nerve function. One of the most debilitating visual conditions following a TBI is diplopia. Strabismus can often occur following lesions affecting cranial nerve 3 (oculomotor nerve), 4 (trochlear nerve), or 6 (abducens nerve). These lesions can occur from blunt head trauma affecting origin, insertion, and or innervation of the extraocular muscles, trauma to brain stem, midbrain or cortex, vestibular trauma, and/or trauma affecting orbital structure and orbital space occupying lesions (21, 39). Often, as is the case, CT scans and MRI are unable to detect lesions related to these specific oculomotor neurons. The authors have previously suggested a dysfunction of the ambient visual process and the lack of feedforward support for peripheral fusion lock.

The inability to provide spatial information will cause a highly focalized nature of vision. In turn, the visual world becomes fragmented. This causes increased concentration on detail and yields increased fragmentation of the visual world. The result can be diplopia that will be characterized and measured by strabismus (exotropia, esotropia, hypertropia, hypotropia). When an individual has diplopia, the spatial reference by which to use vision to lead posture, balance, and motor function is compromised. In turn, it can affect cognitive-perceptual processing due to the distracting influence of physiological stress. In one study (2), the second most common symptom was that 30% of the subjects experienced diplopia following a TBI.

The most common result of lesions of the cranial nerve following a TBI is third nerve palsy. A third nerve palsy is associated with exotropia as well as ptosis and mydriasis of the pupil on the affected side with complete compromise. In most cases, the affect is incomplete causing

variations from decompensated exophoria to intermittent exotropia. Diplopia depends on visual fatigue and chronic development of suppression. Vertical palsies resulting from the affect of cranial nerve 4 will produce hyperphoria and hypertropia as well as decompensation in specific gaze direction and head tilt. Sixth cranial nerve palsy interferes with abduction of the related eye, causing esotropia.

A variety of cranial nerve and binocular function tests are designed to provoke oculomotor failure causing decompensation of binocularity. These tests are described as follows:

1. **Cover Test:** The examiner will perform this test with the patient first fixating on a distant target (ten feet or beyond) and then at a near target (40 cm). The Alternate Cover Test is done by passing a cover alternately from one eye to the other and observing the movement of the eye emerging from under the cover. A heterophoria can be elicited. If observed, the examiner will perform a Cover Test by covering and uncovering each eye to discern from a tropia.
2. **Krimsky Test:** This is similar to the Cover Test, however, compensating prism is introduced to neutralize the motion of the phoria or tropia to determined the extent of deviation.
3. **Bielchowsky's Head Tilting test:** Cranial nerve and oculomotor function is analyzed by having the patient hold fixation in primary gaze while the examiner rotates the patients head first to the left and then to the right testing 3rd and 6th nerve function. The patient's head is moved in extension and flexion and tilted first to the right shoulder and then to the left shoulder to evaluate 4th nerve palsy affecting over and under-compensating oblique muscles.
4. **Lancaster Red/Green Test:** The patient is given glasses in which the OD has a red lens and the OS has a green lens. The examiner holds a red flashlight and the patient holds a green flashlight. The examiner shines the red flashlight on a screen and moves it into the nine cardinal gazes of fixation while asking the patient to superimpose their projected green light on the red light. Any deviation in a particular gaze direction will be noted and related to an underactive, overactive, or restricted ocular muscle.
5. **Red Lens Test:** The examiner holds a red lens before one of the patient's eyes and the patient is asked to fixate on a penlight. If the patient reports seeing two lights, the test is positive for diplopia at the respective working distance.
6. **Worth Four Dot Test:** The patient is given red/green glasses to wear while looking at the projection of four dots that form a diamond. The top dot is red, the inferior dot is white, and the lateral dots are both green. If the patient is binocular, four dots will be

seen. If binocularity is compromised and the patient reports seeing five dots, diplopia has been elicited. If two or three dots are observed, a corresponding suppression is present.

7. **Maddox Rod Test:** The examiner holds a cylinder before one of the patient's eyes while the patient observes a penlight. The eye behind the cylinder will see a vertical or horizontal line of light depending on how the cylinder is positioned. If the line is reported to either the left or right side of the light, a heterophoria or tropia is present at the respective working distance. If the line appears above or below the light, a vertical deviation has been elicited.

Binocular dysfunctions often present as convergence insufficiency or strabismus of which exotropia is the most common following a TBI. This can cause diplopia. The diplopia can be masked by intermittent suppression or accompanying field loss (i.e. homonymous hemianopsia). Any interference with binocularity will affect stereopsis and depth perception. In addition, oculomotor disturbances will affect pursuit tracking, saccades, and fixations.

For those experiencing blurred vision at near, accommodative insufficiency or accommodative spasms have been found as an interfering mechanism causing the related symptoms. Studies have also related binocularity with the neurological correlates such as cranial nerve palsies (35).

The term divergence paralysis was first described by Parinaud in 1883. Relative to TBI, the literature emphasizes the third nerve palsy as being the cause of the majority of those with exotropia following a TBI (34). Other types of neurological disorders affecting binocularity are sixth nerve palsies causing esotropia and fourth nerve palsies affecting vertical imbalances.

Sensory motor and binocular analysis should be performed to evaluate oculomotor function. Assessment should use quantity of function to analyze any limitations of oculomotor movements as well as quality of function (assessing fixation losses and difficulties encountered with pursuit tracking or saccadic fixations into particular fields). This may relate to oculomotor palsies. The assessment of convergence and accommodation quantitatively as well as qualitatively will enable the clinician to begin to understand levels of visual stress in performing visual skill activity (23).

The refractive sequence will objectively and subjectively analyze refractive error as well as variations in refractions which may relate to an unstable nature of accommodation and/or subluxation of the accommodative lens following trauma to the eye or head. Careful analysis of eye muscle balance through phoria, vergence, and duction testing will provide the clinician with an understanding of states of eye muscle balance and muscle reserves related to dysfunction of ambient and focal

processing. More specifically, a dysfunction of the ambient visual process will cause a lack of spatial support, thus affecting phoria, duction, and/or vergence measurements causing PTVS. In the most severe condition, exotropia can be produced, which is also known as third nerve palsy.

Surgical intervention has been used to affect oculomotor paresis. However, the success from surgery can be compromised if there is interference with the ambient spatial feedforward to binocular cortical cells (23).

The use of botulinum toxin has been found effective in reducing over action and muscle spasticity in affecting general muscle tone in the body as well as in cases of oculomotor spasm (45).

Pupillary assessment can offer an understanding of interruption of afferent and efferent sensory pathways (46). Defects in pupillary function can cause variations in response such as with the Marcus-Gunn pupil (47). Dilation of the consensual response indicates asymmetry in the conduction of afferent sensory fibers anterior to the chiasm and it differentiates a unilateral occurrence.

Wernicke's hemianopic pupil is another method by which to differentiate homonymous hemianopsia of tract lesions from the homonymous hemianopic lesions occurring in optic radiation dysfunction. The pupil sign demonstrates an inappropriate or impaired reaction in both pupils when light is specifically delivered to the amourotic half of either retina (47). Parinaud's syndrome can occur following a TBI and is characterized by displaced pupils, ptosis, nystagmus, oculomotor palsies (limitation of supraduction), papilledema, as well as producing symptoms of vertigo and ataxia (48). Papilledema and optic nerve atrophy are also characteristics that should be carefully evaluated through direct and indirect ophthalmoscopy (48).

## PSYCHOPHYSIOLOGICAL TESTING

Evaluation of visual function is important to identify lesions for the purpose of diagnosis and prognosis of treatment in visual problems following a TBI. Two kinds of examinations, psychophysiological and electrophysiological, allow assessment of the disorders in the entire length of the visual pathway. The following is a description of psychophysiological testing.

### Visual Acuity

Acuties should be functionally based and objectively based. The assessment of visual acuity should be performed both monocularly and binocularly. The standard Snellen Acuity Test can be performed at six meters and forty centimeters. However, other types of tests may be more appropriate if there is vision impairment present.

Tests such as the Feinbloom charts and the Sloan Acuity Charts may offer more precise measurements.

Behavioral assessment and functional variations should be noted such as a monocular acuity that is better than a binocular acuity. Often, interferences with contrast sensitivity following post-trauma vision syndrome will affect acuity in varying environmental conditions (49).

Visual acuity and visual field assessments are routinely psychophysiological tests. However, motion perception is also one of the elementary visual phenomena, especially in the affect from neurological trauma.

*Visual Field* Also important is a careful assessment of the visual field (50, 51). Visual field is an island or hill of vision in a sea of darkness (Figure 29-1). When visual defects occur, the corresponding part of the island is lost. The field of vision at any particular sensitivity level is changed.

Abnormalities of any point along the visual pathway affect the visual field, often in a pattern characteristic of a particular disorder process or location. The visual field defects in the visual pathway correlate with the lesion sites and field defects. Homonymous refers to a defect present in both eyes with the same laterality, while heteronymous refers to visual loss that usually respects the vertical meridian. Congruous fields are symmetric in both eyes. The lesions of upper or lower occipital banks produce quadrantanopia defects, while lesions within the temporal and parietal lobes cause field defects that tend not to respect the horizontal meridian.

More sensitive and precise evaluation of visual field can be obtained by automated and computerized threshold perimeter or kinetic testing of Goldmann perimeter. In many instances, the computerized threshold perimetry is a more reproducible test for patients with defects on optic neuropathies, chiasmal disturbances and so on. Computerized threshold perimeter performs static threshold

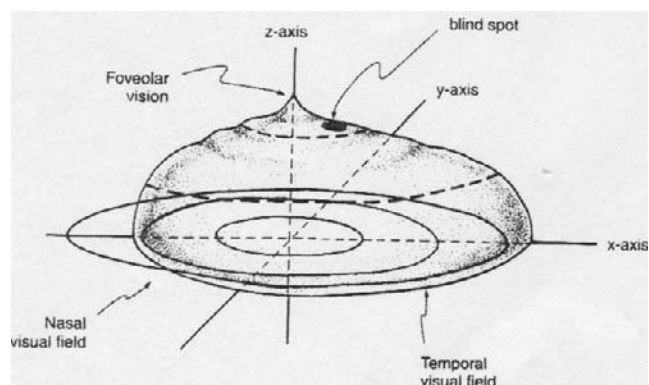


FIGURE 29-1

Visual field is an island or hill of vision in a sea of darkness (57)



measurement. New statistical software empowers the user with additional means of refining the assessment and representation of visual field.

The Goldmann perimeter allows interaction with the examiner and may be more appropriate for patients with neurological impairments. It is a substantially more sophisticated method of field assessment. Kinetic perimetry is usually the preferred method. It involves moving the target from a non-seeing area into a seeing area. A contour map of the island of vision can thus be established by using targets of varying size and brightness. Computerized perimetry is currently the more popular test method in visual field testing.

The visual field must be tested for each eye separately. The visual field is a dynamic area that changes according to a large number of variables. It should always keep in mind that all modalities for visual field evaluation are subjective and depend on the patient's level of alertness, cooperation, ability to fixate centrally, and response rapidity.

Visual field assessment should include standard objective instrument measurements of threshold visual fields when possible, but persons with traumatic brain injury may not be able to sustain attention and organization for a purposeful evaluation in automated field tests. Confrontation visual field assessment which will include holding the person's gaze while presenting objects in the peripheral field are effective as well as a saccadic confrontation visual field assessment. The latter can be used effectively for individuals who cannot hold fixation and are peripherally distractible.

The methods for this form of testing are to provide stimuli or targets in various portions of the field. The examiner observes the functional behavior of the patient as they shift their eyes via saccadic movements into the various visual fields. This may be performed monocularly as well as binocularly.

Homonymous deficits often will relate to spatial problems affecting posture and balance. Visual field neglect is a condition in which there is no hemianopsia, but spatial information in the affected field (usually the left visual field) is ignored (24). Dysfunction caused by field loss will be discussed later in this chapter.

*Motion Perception* Motion perception is as elementary a visual perception as form or color senses (52). It includes three-dimension stereo-sense, location, and layer sense. The projected pathway of motion perception is from retinal sensory cells through ganglion cells, lateral geniculate body of thalamus to striate cortex. The abnormalities of motion perception have been seen in optic neuropathy and glaucoma and it was also reported that motion perception decreased or diminished in cerebral traumatic patients with normal visual acuity or color perception.

Three methods for evaluating motion perception are used: 1) using the motion stimuli of the random dots; 2) using the stimuli of sinusoidal grating strips; and 3) using bar target stimuli. The bar targets projected on a monitor can be observed clearly and distinguished easily by subjects. The size and density of bar targets as well as variations in direction of the bars and flickers can be controlled (vertical, horizontal, and oblique).

## ELECTROPHYSIOLOGICAL TESTING

Most electrophysiological tests are evoked responses for which adjusting stimulus conditions and techniques of recording makes possible a representation of the sequence of events along the visual pathway (53–55). Besides international standards of ERG, PERG, EOG, and VEP, it is necessary that each laboratory should have its own normal data to evaluate patient's response recording because the amplitude and implicit time of wave may vary among laboratories.

### Visual Evoked Response (VEP)

Visual evoked response is a measure of the electrical activity through the visual cortex. Certain conditions are required for VEP measurement: visual stimulus, scalp electrodes, amplifier, averaging system, and recording equipment. The electrodes are positioned in the midline at the occipital and posterior frontal region. An electrode placed on the ear provides a ground.

VEP is response to stimulation by flashes or pattern stimuli with alternating checkerboard or stripes on a monitor. The flash VEP is applied in the persons with very poor vision. A full field Ganzfeld stimulator is used for flash stimuli. The pattern stimulus is preferable when the eye is optically correctable, since the occipital cortex is more sensitive to sharp edges and contrast, while it is relatively insensitive to diffuse light.

The VEP is characterized by the waves N, P, N, and P. The amplitude and implicit time of the wave depends on the check size, contrast, and frequencies of the stimulus. The temporal aspect (latency) of the VEP is more reliable with the significance in clinical application of acuity and focalization, however, the amplitude of VEP under binocular assessment has more relevance to ambient spatial relationships.

The VEP traditionally has been used to confirm the diagnosis of neuropathy in the visual system. It assesses disorder of optic nerve fibers, estimates visual acuity in nonverbal and verbal persons, evaluates potentials for reasonable visual acuity in some kinds of patients, and detects and locates visual field. In some cases, the VEP is even more sensitive for detecting compressive lesions than subjective perimetry.

## Multifocal Visual Electrophysiology

### *Multifocal Electroretinogram (mfERG)*

*Multifocal Evoked Response (mfVEP)* In 1992, Sutter and his co-workers reported presenting pseudorandomly multifocal stimulation together with retinal or cortical scaling of the size of the stimulated areas. They were able to stimulate numerous locations of the visual field simultaneously and to extract individual responses from each of them. The electrode permitted the recording of reliable responses from numerous retinal locations such as areas 61, 103, 241 loci of the visual field. This work establishes the multifocal electroretinogram (mfERG) and multifocal visual evoked response (mfVEP) with field topographic mapping of ERG or VEP components.

The mfERG or mfVEP is based on the Wiener kernel expansion and uses deterministic pseudorandom binary m-sequence stimulation. It permits computation of the signal by cross-correlation of the response evoked by m-sequence stimulation with m-sequence itself. Therefore, it is very effective for mapping.

The technique allows computation of the first order or higher order kernel which characterizes the nonlinear interaction between visual events. The amplitude of the averaged quadratic VEPs is in proportion to visual field losses. The mfERG or mfVEP is a powerful method for the investigation of brain activity and mechanisms of human visual perception.

Electrophysiological analysis through use of binocular visual evoked potentials assesses the relationship of support for focal processing by the ambient (spatial) system (10).

The visual evoked potential should be performed with habitual corrective lenses. A P100 cross-pattern reversal analysis is performed. Following the initial response, two diopters of base-in prism in conjunction with binasal occlusion should be introduced before both eyes in addition to the corrective lenses. The amplitude and latency of the P100 should be compared. An amplitude increase following the introduction of base-in prism with binasal occlusion is seen as a test positive for PTVS (11).

*Electro-Oculogram (EOG)* The EOG technique of recording eye movement is widely available and reliable. Since the eye acts as a dipole, the electrical current changes are caused between the cornea and posterior pole of the eyeball when the eye is moving in different directions. The EOG is performed by placing four cutaneous electrodes are placed on the canthal regions of both eyes. An electrode placed on the ear serves as the ground. The potential is recorded when alternate fixations or target movement is performed. Changes in illumination, skin resistance, and speed of the target will affect the results of the EOG. The EOG can yield reasonable recordings of horizontal movements, however,

vertical movements may be affected by eyelid blinks and nonlinearities.

Observation of eye movements by the clinicians provides a simple qualitative assessment and in most cases is able to identify most abnormalities. Therefore, the EOG is used to distinguish the affects of specific ocular modalities and to determine the presence or absence of improved motor function during therapy for visual pathways.

## NEURO-MOTOR ASSESSMENT

The neuro-motor assessment can be performed to evaluate the role of the ambient visual process in establishing concepts of visual midline and how it affects posture, balance, and movement. Concerning posture, dysfunction of the ambient visual process will also affect seating position and posture.

The visual midline test may be performed in those individuals that can respond actively (10). Observation of the patient in a seated position as well as during ambulation should be performed to evaluate the correlation of the visual midline shift test to tendencies to drift to one side and/or lean forward or backward during ambulation. Lateral shift of the visual midline will often cause a lean or drift during ambulation. An anterior shift can cause a lean or flexion forward. In more severe cases of the anterior shift of visual midline, toe-walking will develop in an attempt to compensate for the imbalance. A posterior shift of visual midline will cause an extension posture and tendency to lean backward in retropulsion.

## VISUAL-VESTIBULAR INTEGRATION DYSFUNCTION

There are numerous treatises that discuss the anatomy, physiology, and treatment of the separate visual, vestibular, and sensory motor systems, however, until recently, few were able to discuss the functional integration and relationships that exist between these three systems. Dizziness, vertigo, and imbalance are common symptoms following a TBI and often indicate miscommunication between these systems. Inner-ear disorder of the vestibular system is a common diagnosis, however, the relationship to the visual process is often overlooked or misinterpreted.

Coordinated movement involves a complex interaction between sensory afferents from the visual system, somatosensory system, and the vestibular system. In particular, the semicircular canals and utricle/sacculle respond to rotational and linear/gravitational information and is transmitted via the vestibule-cochlear nerve through the ascending and descending axon branches of the brainstem vestibular nuclei. At times, vision supercedes or enhances vestibular input. The vestibulo-ocular reflex

(which maintains foveal fixation during head movements), the vestibulospinal pathways (which are responsible for postural control under static and dynamic circumstances), and the vestibulocerebellar pathways (allowing for modulation of motor output via the flocculonodular lobe of the cerebellum) are all integrated at this level of the brainstem.

The vestibular nuclei accept information from the visual system relative to the ambient visual process to support movement and visual interaction of the environment. The subset of the ambient process, the magnocellular system, provides information about perception of contrast and movement involving short wavelength and low and middle spatial frequency input. This affects awareness of depth perception, motion detection, and alterations in brightness. The parvocellular system is mostly responsible for detail discrimination, color perception, and identification of patterns or shapes.

An important differential between magnocellular and parvocellular processing is that the former is responsive to the onset and offset of receptive stimuli, whereas the latter is responsive to longer stimulus duration. Parvocellular input projects to the occipital lobes along the retinal-geniculate-cortical pathway and then may send axons to the temporal brain region. It is the ambient process inclusive of the magnocellular system that supports posture, balance, and spatial orientation. Information synapsing in the occipital lobe will proceed to temporal and parietal lobes for higher level processing while the information from the superior colliculus will integrate with head and body postural reflexes flowing through the vestibulospinal and vestibulocerebellar tracts.

The vestibulo-visual relationship supports a stabilization of vision during movement of the head, neck, or body. Diplopia is the most frequently considered symptom of disruption in this interaction in addition to other interferences with binocularity.

The significance of the vestibulo-oculo-cervical triad is the quality and organization of somatosensory input (20) which occurs in the thalamus and is transmitted to the cerebellum and primary somatosensory cortex within the parietal lobe. Multisensory integration and conscious perception occur as this information is projected into the secondary and association cortices of the frontal, temporal, and parietal lobes where the perception of dizziness, vertigo, or imbalance may be the result.

A complete medical history with careful analysis of the visual process and vestibular system is necessary for diagnosis and prognosis. Too often, functional vestibular rehabilitation for vertigo and dizziness is begun before the relationship to visual processing problems is determined. Under the age of fifty, TBI is the most common cause of dizziness and vertigo from a direct head trauma and whiplash.

Differential diagnosis for dizziness without vestibular dysfunction includes PTVS, hyperventilation, dehydration,

orthostatic hypotension, vasovagal syndrome, arteriosclerosis, osteoarthritis, and central nervous system disorders. A Group II Disorder such as aortic, carotid, vertebrobasilar, subclavian, and cerebral artery insufficiency should be ruled out.

Once a Group II disorder has been ruled out, vestibular anomalies such as vestibular neuritis (acute labyrinthitis), benign paroxysmal positional vertigo (BPPV), nucleo-reticular vestibular syndrome, Meniere's Disease, Perilymphatic Hypertension, and Perilymphatic Fistula should be ruled out.

Since destabilization of the ambient process following trauma has been clinically found to cause vertigo and dizziness which are symptoms of PTVS. By treating PTVS, stability is created in ambient visual processing, thereby increasing the efficiency of matching information with vestibular, kinesthetic, and proprioceptive processes. This, in turn, frequently reduces or eliminates symptoms of vertigo and dizziness.

### VISUAL FIELD DYSFUNCTION

A visual field loss is relative to the area of cortical lesion or optic nerve insult. Field defects that occur beyond the optic chiasm will always cause a homonymous hemianopsia not necessarily congruous (56). Depending upon the area of the cortex affected, geniculate lesions are often not suspected and are rarely diagnosed. However, in the case of a homonymous hemianopsia involving primarily the central visual field sparing the peripheral field, the geniculate body should be considered as the source.

Temporal lobe lesions will often produce an incongruous superior quadrantanopsia with a sloping margin. In addition to field loss, parietal lobe lesions cause a lack of awareness of the field loss. It can be differentiated by confrontation visual field assessment when the clinician presents simultaneous targets in opposite fields. The parietal lobe lesion will cause an extinction phenomenon yielding a person to be aware of only one target at a time. If the target is moving in both fields, often the extinction phenomenon will not occur. The target must be stationary in order to demonstrate the possibility of a parietal lobe lesion. The common defect is an inferior homonymous quadrantanopsia.

Occipital lobe lesions are characterized mostly by their congruous nature. These can encompass the entire hemianopic field or portions thereof depending on the specific location of the lesion. Riddoch's phenomenon described in 1917, involves the inability to see stationary objects presented on the affected side but could see objects that were moving. Recent research related to focal and ambient visual processing suggests that the ambient visual process is a survival system that particularly responds to movement in the peripheral vision. Perhaps an additional

interpretation from the original one would be that areas of the lesion are being circumvented when feedforward occurs from the ambient visual process. However, when stationary targets are presented to those with PTVS in conjunction with a field loss, it will cause them to over-focus on the sensory component of the target they are looking at. This over-focalization and lack of an ambient feedforward response can possibly cause a condition related to field neglect and/or extinction phenomenon.

Like visual field loss, visuospatial neglect may manifest as a complete loss of visual perception on the side affected or as a relative loss where less is perceived in the neglected field particularly when there are competing stimuli in the opposite hemifield (57). With appropriate treatment, the functional effect of the hemianopsia and/or neglect can be minimized. Patients with visual field loss who do not receive training, rarely use adaptive search strategies (58). Training the patient to scan into the area of loss, in some cases, creates incomplete recovery of visual field (59–62). Zihl and von Cramon (63) have reported extensive field recovery taking place only during periods of appropriate treatment. Patients with visuospatial neglect require additional training to gain skills for compensation for many activities of daily living.

A homonymous hemianopsia can be functionally very debilitating to the patient in rehabilitation. Not only does it represent a complete loss of visual field, but it also affects concepts of midline. The concept of visual midline shift syndrome is an important one to understand relative to visual motor rehabilitation for any person following a TBI, but particularly for those who have suffered a homonymous hemianopsia. When the visual midline shifts and the individual begins to lean in the direction of the midline, the sensory stimulation from the proprioceptive, kinesthetic, and vestibular system will reinforce the lack of weight bearing on the paretic side. In turn, this also reinforces the development of spatial neglect.

To counter the compressions and expansions that distort spatial perception following TBI, prisms can be effectively used. A prism is a wedge of glass or plastic. Optically when one looks through a prism, the image of what is being looked at appears to be shifted toward the apex or thin edge of the prism and away from the base or thick edge. The shift in image occurs because the prism expands space on one side and compresses space on the other. The prism expands and compresses in a three dimensional manner, but for the purpose of this discussion let us consider it only two dimensionally. The prism can be used to alter the distortion of space caused by a visual midline shift if placed in the appropriate direction before each eye. This is termed a yoked prism system. The amount of prism can be varied depending upon the amount of distortion in the visual process. Yoked prisms are an effective means by which to shift the concept of visual midline, but also should be used in conjunction

with other methods of field enhancement or to increase awareness in the affected homonymous hemianopic field.

An enhanced sector prism system is used to affect homonymous hemianopsia by increasing awareness of peripheral visual fields on a sensory level, whereas the yoked prism is used to affect VMSS sensory motor level. The enhanced sector prism system (mounted binocularly or monocularly) is positioned to the side of the line of sight in a spectacle frame with the base end of the prism positioned temporally in the direction of the hemianopic field. When looking into the prism(s), the image will be shifted toward the apex enabling the individual to see objects to the side they would normally not be able to see unless they took a significant eye and head turn in the direction of the hemianopic field. Many individuals with a homonymous hemianopsia frequently bump their head and body on objects that they did not see. This causes numerous bruises as well as the possibility of more significant injuries.

The experienced clinician will recognize that individuals who have a visual midline shift syndrome as well as a homonymous hemianopsia will often have difficulty adapting to the use and succeeding with an enhanced sector prism system because the midline reinforces the spatial neglect. Therefore, treatment with yoked prisms for VMSS is necessary prior to or in conjunction with an enhanced sector prism system. By addressing the issue of VMSS, the success of rehabilitation with an enhanced sector prism system will be increased. The combination of yoked prism in the carrier lenses as well as the sector field prism positioned appropriately laterally to the line of sight can be an effective combination. Rehabilitation with yoked prisms to treat visual midline shift syndrome will directly affect field neglect as well as VMSS. Training can then be established to utilize the enhanced sector prism systems (49, 64). In other cases of visual loss including trauma with constricted visual fields, single or multiple prisms are used mounted laterally on each lens (65).

Sector prism systems used to increase a patient's peripheral awareness can be made out of Fresnel press-on prisms (66). Peli (67) reported that the press-on sectoral prisms when applied to the upper and lower part of the spectacle lens causes a refractive exotropia and thus improves simultaneous awareness and greater obstacle avoidance. However, due to the poor optical quality of the press-on Fresnel prisms, sometimes patients experience a decrease in acuity, or have problems with reflections or distortions which negatively affect the patient's acceptance and success (66). Gottlieb, et al. (65) found that press-on prisms sometimes even decreased a patient's tendency to scan into their field of neglect due to their dislike of looking through these prisms and hence amplified avoidance of this area.

Complex visual loss is no longer an insurmountable obstacle in the way of effective rehabilitation and recovery

of function. Using technology along with proven rehabilitation strategies can aid in meeting the goals of the patient and rehabilitation team.

Literature reinforces that enhanced sector prism systems yield fewer mishaps of bumping into objects or people and their fear of collisions notably decrease (68, 69). The primary result of this improved function is an increase in safety and secondarily a decreased risk for insult and injury (70). In the long term, a patient may experience some recovery of vision in the hemianopic field (49). In a study by Gottlieb, Freeman, and Williams in 1992, 27 of the 34 patients who had been fitted with enhanced sector prism systems to use them full or part time over the next 2.5 years. The prism used in this study increased the patient's peripheral field awareness an average of 13.25 degrees.

### VISUAL PHENOMENA ASSOCIATED WITH TBI

Visual phenomena following a TBI can be quite diverse. Sometimes these phenomena are bizarre and assumed to be of psychological nature. Some of these symptoms will be visual hallucinations, flashing lights, palinopsia, variations in homonymous field defects, and scintillating scotomas. It has been reported that visual hallucinations can be associated with temporal and parietal lobe lesions. Following a TBI, individuals may report hallucinations that take several forms. Some individuals will experience movement of the visual field. Sometimes, the entire visual field will appear to shift or move as they move their eyes or body. Others will report seeing movement in their peripheral vision but when they turn to look, they find only stationary objects. Another common hallucination is seeing things or persons in the periphery and/or central vision. Some patients report seeing snakes dropping from the ceiling or wriggling across the floor. Others will perceive strange type of creatures appearing to move and shift.

Many of these phenomena are reported by persons who have PTVS. It has been found clinically that treatment for post-trauma vision syndrome will often stop the perceived hallucinations (23). Although it has been noted in literature that parietal and temporal lobe lesions as well as occipital lobe lesions can be the cause of these hallucinations, it has also been suggested that some of the hallucinations may be due to psychiatric disorders. It is not uncommon for persons following a TBI who are experiencing hallucinations to be placed on psychotropic medications. It is the author's experience that many of the hallucinations will persist even though these medications are being used.

One possible explanation for the existence of hallucinations following TBI is that when there is dysfunction to the ambient visual process, the ability to stabilize

the retinal image is compromised. The superior colliculus is responsible to a great extent for providing the spatial matched information for ambient and sensory motor processes to the occipital cortex but more specifically, to provide a stabilization of the peripheral retina. When the ambient visual process is compromised, the visual processing system that remains, the focal process, isolates to detail but does not have a spatial grounding to stabilize the retinal image.

It has been noted clinically that persons experiencing PTVS will perceive words on a page or objects in the field appear to move when they perform movements of their eyes such as saccadic fixations. Saccadic fixations in a field of vertical lines will produce a shimmering movement of the vertical lines. The lines will appear to move in various manners similar to the movement of a snake. It is hypothesized that at least some of the hallucinations experienced following a traumatic brain injury are due to the unstable nature of the ambient visual process in PTVS. The interpretation of 'snakes' and other objects appearing to move are perceived movement of vertical and horizontal lines in their environment due to the unstable nature of the peripheral retina related to the compromise of the ambient visual process. It has been found clinically that by treating individuals for PTVS, the hallucinations will often cease within hours to days.

### BINOCULAR INTERVENTION

Treatment for diplopia varies depending upon the philosophy of the treating doctor as well as the rehabilitation program. Some do not recommend any treatment and choose to wait to determine if time will be the healing factor. Others recommend patching of the deviating eye to eliminate the diplopia, whereas others recommend patching of the fixating eye in order to stimulate fixation in the eye that is deviating. The lack of any treatment approach and often an inappropriate treatment regimen for a person in a state of diplopia can and will interfere with all aspects of rehabilitation.

The visual process is the dominant and primary sensory motor system affecting all aspects of posture, movement, balance, as well as cognitive-perceptual function. Vision works to reinforce all that we do. If vision is dysfunctional, it will interfere with all performance.

Failure to eliminate diplopia can directly affect the outcome of rehabilitation which financially is being undertaken at tremendous costs by insurance programs as well as individual funding from families and relatives. Therefore, in view of the limited amount of time for rehabilitation and the extraordinary amount of money that is often spent to rehabilitate the person, it is logical to attempt to rehabilitate the condition causing diplopia through treatment of PTVS, compensating prism, and/or

vision therapy. It has been suggested that surgical intervention, while possible, is at best a challenge for treating diplopia following a traumatic brain injury (44).

### **Pathophysiology of Injuries Contributing to Diplopia**

Injury to the visual system can be diffuse and/or focal and can localize to any, or a combination of the ocular structures, cortical areas, midbrain, or nerve nuclei. Brain injuries affecting vision typically occur via axonal shearing, hemorrhage, infarct, inflammation, and/or compression. Ophthalmoplegias (cranial nerve palsies) may completely, or partially involve any single or all three of the nerves controlling ocular motility.

The third nerve controls the medial, superior and inferior rectus muscles, inferior oblique, ciliary body, levator, and papillary sphincter muscles. Clinically, a complete acquired CNIII palsy will present with ptosis, hypoexotropia, dilated and fixed pupil, paralysis of accommodation and limitation of gaze on the affected side. Partial involvement can be any combination of, but not all of the above. Spontaneous recovery, if any, is usually within six months.

The sixth nerve controls the lateral rectus muscle. Clinically, the patient will have an esotropia in primary gaze that increases as they attempt to look towards the affected side. There is a limitation of gaze to abduction of the affected eye. Spontaneous recovery, if any, is usually within six months.

The fourth nerve controls the superior oblique muscle. Clinically, the patient will present with their head tilted to the contra-lateral side in an effort to offset cyclical, or torsional movement of their eyes. Spontaneous recovery, if any, usually occurs within six months.

### **Vision Rehabilitation**

*Vision Therapy.* Vision therapy (also referred to as vision training or orthoptics) is a clinical approach to treat a variety of visual disorders including certain strabismic conditions. The practice of vision therapy uses a variety of non-surgical procedures to modify the visual process affecting function. By first evaluating the bimodal processing of vision, the doctor will establish a plan of treatment designed to affect balance between the focal and ambient visual processes as well as the ability to match information with sensory motor systems. The goal is to improve the visual process and affect binocularity, spatial organization, balance, movement, etc.

Vision therapy will typically involve a series of treatments. During treatment sessions, individually planned activities are conducted under optometric supervision. The specific procedures and necessary instrumentation are determined by the individual patient's needs and the

nature and severity of the diagnosed problems. Vision therapy techniques employ the use of lenses, prisms, computers, biofeedback, stereoscopic devices, and a variety of other instruments and techniques designed to affect the visual process.

*Prism Rehabilitation* As mentioned previously regarding VMSS and visual field loss, prisms are ophthalmic tools that refract light while also compressing and expanding it. Prisms are used clinically in a therapeutic manner to reestablish balance of ambient and focal visual relationships causing visual dysfunction or in a compensatory manner to offset the affects of a binocular imbalance.

In binocular and strabismic dysfunctions, use of prism can reduce symptoms, improve function, and hasten recovery. In these situations, prescription of therapeutic prism (an amount, type, and orientation of prism to reduce or neutralize the binocular/vision dysfunction or to stimulate visual function and fusion) can help reduce or eliminate symptoms and aid treatment. To affect spatial imbalance caused by ambient and focal dysfunction (see PTVS and VMSS), yoked prisms are prescribed.

There are times, patients, and situations when remediation of a visual problem is not possible or feasible. In these situations, prescription of compensatory prism (an amount, type, and orientation of prism to reduce or neutralize the binocular strabismic dysfunction) can help reduce or eliminate diplopia.

*Patching.* Patching has frequently been used to eliminate diplopia (21, 71). While effectively eliminating diplopia, patching renders the patient monocular. The chief problems of monocular vision are loss of stereopsis, reduction of peripheral visual field, and VMSS (10, 21, 72).

Monocular vision reduces the field of vision by approximately 25%, decreases stereoscopic vision, decreases visual acuity (due to lack of binocular summation), and impairs spatial orientation. Monocular versus binocular individuals will have a disadvantage in visual motor skills, exteroception of form and color, and appreciation of the dynamic relationship of the body to the environment which facilitates control of manipulation, reaching, and balance (44).

Problems arising from acquired monocular vision will manifest as difficulties in eye hand coordination, clumsiness, bumping into objects and/or people, ascending or descending stairs or curbs, crossing the street, driving, various sports and other activities of daily living which require stereopsis and peripheral vision (72).

In the case of diplopia following TBI, a standard recommendation in acute care facilities and rehabilitation hospitals is to patch one eye. As discussed previously in the section about VMSS, this will cause and/or reinforce a shift in concept of visual midline affecting posture and balance as well as having an adverse affect on physical/occupational therapy.

Patching can be performed but should be done with respect to the ambient visual process. A central occlusion patch can be placed on the deviating eye. For example, if there is a left exotropia, vertical adhesive tape can be placed in front of the deviating eye so that it is built from the nasal portion of the eyeglass frame out to just block the center of the pupil or line of sight. In this way, diplopia will be eliminated when the person looks directly at something, but the peripheral field of the deviating eye is respected by not covering it. In turn, it allows the ambient visual process of both eyes to begin to match information with other sensory motor systems. This will support visual midline concept for posture, balance, and ambulation.

Another method involves use of a partial and selective occlusion. The spot patch is a procedure that eliminates diplopia without compromising peripheral vision (73). It is a small, usually round or oval patch made of adhesive tape, blurring film, or other filters. It is placed on the lens of glasses and directly in the line of sight of one eye. The diameter is generally about one centimeter, but will vary on the individual angular subtense required for the particular strabismus, ophthalmoplegia, or gaze palsy. Final size and placement is determined by evaluating different sizes and shapes to arrive at the smallest one which effectively eliminates the diplopia. If there is a paresis, the spot patch should be placed in front of the affected eye.

By eliminating diplopia through central occlusion, the ambient process becomes more effective and supportive. The spot patch is indicated in cases of intractable diplopia where other methods of treatment are either not viable, have failed, or are contraindicated. Examples of such cases include refractory, third nerve ophthalmoplegia, sixth nerve palsy, and inter-nuclear ophthalmoplegia. Central occlusion is effective if the diplopia is constant and the patient exhibits relief and improved general function as a result of eliminating the diplopia.

Determining size, shape, and placement of a central occlusion patch requires measuring the diplopic field, determining limitation of ocular motility, and measuring the angle of strabismic deviation.

## CONCLUSION

Rehabilitation of a person with a traumatic brain injury requires applying the science of understanding neurological dysfunctions as they pertain to interference with motor, sensory, and cognitive processes. Until recently, if a person suffered visual dysfunction in the way of binocular, spatial perception, and/or perceptual motor dysfunction, rehabilitation treatment was limited to patching of the deviating eye causing diplopia or primarily hospital based occupational and physical therapy.

Recent research has demonstrated that often traumatic brain injury affects visual processing which can cause

or relate to the performance dysfunction as well as binocular problems. Neuro-ophthalmology has provided an important means of intervention for neurological problems affecting the visual system. Diagnostic assessment through use of electro-physiology analysis in addition to the state of the art assessment through MRI and CT scan enables a neuro-ophthalmologist to function as a critical member of a multi-disciplinary team serving the person with a TBI. A careful evaluation of cranial nerve function and abnormalities is essential for establishing the diagnosis as well as determining appropriate neuro-medical recommendations for treatment. A range of options are available such as utilizing medications, botulinus toxin, and surgery.

Experience has shown that skilled optometrists familiar with the practice of neuro-optometric rehabilitation can be an important contributing member to the rehabilitation team. The skills of the optometrist are in applying the new science and understanding of the bimodal process of vision to the art of visual rehabilitation. The neuro-optometric rehabilitation evaluation involves the careful analysis of binocularity and spatial and perceptual motor function related to dysfunction between the ambient and focal visual processes by utilizing a variety of techniques incorporating lenses, prisms, and sectoral occlusion. The optometrist can affect performance and function at the appropriate critical stages of rehabilitation not being provided in rehabilitation hospitals and long-term care programs. This does not exclude individuals who are still suffering from binocular and spatial-motor disorders after being released from such programs. Neuro-optometric rehabilitation has been found effective in improving binocularity as well as visual spatial-motor dysfunctions affecting balance and posture by treating PTVS and VMSS years after the neurological insult has occurred.

The role of the neuro-ophthalmologist as well as the optometrist practicing neuro-optometric rehabilitation are important in advancing overall rehabilitation for a person with a TBI. The neuro-ophthalmologist and optometrist will provide critical insights into neurological dysfunction as well as the means by which to rehabilitate the high incidence and prevalence of visual dysfunction affecting performance following a traumatic brain injury.

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# 30

## Cranial Nerve Disorders

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### INTRODUCTION

Cranial nerves provide motor and sensory innervation to the head and neck, and are termed such owing to the fact that they emerge from the cranium. Injury to the cranial nerves is common with traumatic brain injury (TBI). In this chapter the anatomy, pathway, function, injury incidence, mechanism of injury, examination, treatment, and prognosis will be discussed for each of the cranial nerves. Introductory information about cranial nerves and their injury is briefly reviewed before discussing each nerve individually.

The true incidence of cranial nerve injuries is difficult to estimate. The olfactory nerve (cranial nerve I) is reported to be the most often injured, followed next in frequency by the facial and vestibulocochlear nerves, less commonly the optic and oculomotor nerves, and rarely the trigeminal and lower cranial nerves (1). Cranial nerve palsies may occur with TBI for several reasons, including acceleration-deceleration, shearing forces, skull fracture, intracranial hemorrhage, intracranial mass lesion, uncal herniation, infarct, or vascular occlusion. These circumstances may cause insults to the nerves through such mechanisms as compression, traction, transection, or ischemia. Central injury may occur from brainstem or cerebral damage; peripheral injury results from fracture or local injury. Cranial nerves are particularly at risk for injury as they traverse over bony protuberances and

through bony canals, or by direct injury from basilar skull fracture. The cranial nerves most susceptible to injury due to fracture are: olfactory, optic, oculomotor, trochlear, facial, auditory, and trigeminal (first two branches). The site of cranial fractures should indicate to the clinician the possibility of cranial nerve injury.

Injury to the cranial nerves may result in significant consequences to the individual with TBI, which may be further compounded by the deficits caused by cortical injury. Resulting impairments in sensation (sight, hearing, smell, taste) and motor function (facial expression, mastication, swallowing, speech) may impact such things as appetite, safety, interpersonal communication, and cosmesis.

Cranial nerves pass through the brainstem, and thus, abnormality in these nerves may serve as a reflection of injury severity. For example, pupillary, oculo-vestibular, and oculocaloric reflexes have been shown to be strong prognostic indicators of mortality (2–6) and persistent cognitive disability (7).

Diagnosis is generally based on physical examination. Table 30-1 lists the examination tests and supplies for each cranial nerve. In the presence of altered consciousness examination may be difficult and incomplete. Thus, as one recovers from TBI those aspects of the examination that were previously not possible will need to be performed. A good cranial nerve examination can help identify important problems, and direct treatment. Electromyography and nerve conduction studies may aid the clinician in lesion

**TABLE 30-1**  
*Cranial Nerve Function and Examination*

NERVE	FUNCTION	TEST	SUPPLIES
Olfactory (I)	Smell	Evaluate patency of the nasal passages. Then, determine if the person can detect familiar, non-noxious smells with eyes closed. Giving the person choices may help overcome word finding problems.	Odors or smelling card
Optic (II)	Visual acuity; visual fields	Have patient identify # of fingers held in visual fields and read up close and far away	Snelling visual acuity card
Oculomotor (III)	Pupillary reaction; lid retraction; and eye movement	Shine light in each eye to assess pupil reaction; note lid function; test eye movement for upward, downward, & medial gaze	Penlight
Trochlear (IV)	Intorsion and downward eye movement	Have patient follow finger to move eye downward	
Trigeminal (V)	Facial sensation; corneal sensation; chewing function	Test facial sensation for all three divisions; test corneal reflex; hold mouth open against resistance; clench teeth	
Abducens (VI)	Lateral eye movement	Have patient move eyes from side to side, lateral gaze	
Facial (VII)	Facial motor function; lid closure; taste sensation (anterior)	Smile, wrinkle forehead, wink, puff cheeks, close eye tight, identify tastes with anterior tongue	
Acoustic (VIII)	Hearing; balance	Test hearing; assess for nystagmus; finger to nose & heel to knee; Dix-Hallpike; vestibulo-ocular reflex; Romberg; Sharpened Romberg; Fucada Stepping Test; Caloric Stimulation Test	
Glossopharyngeal (IX)	Swallowing; voice	Say "ah"; swallow; test gag reflex	Tongue depressor
Vagus (X)	Gag reflex	Tested above via gag reflex	Tongue depressor
Spinal (XI)	Neck strength	Resist head rotation, shoulder shrugs	
Hypoglossal (XII)	Tongue movement & strength	Stick out tongue; resist tongue movement with tongue depressor	Tongue depressor

localization and prognostication. A range of treatment approaches exist for cranial nerve deficits. With many of the nerve injuries measures should be instituted to avoid secondary injury.

The cranial nerves carry up to six modalities as defined in Table 30-2: general sensory, visceral sensory, special sensory, somatic motor, branchial motor, and visceral motor. The modalities served by each cranial nerve are indicated by color in Figure 1 and are summarized below:

**Sensory Pathways** Three neurons make up the cranial nerve sensory pathways: primary, secondary, and tertiary. The cell bodies of the primary neuron of cranial nerves are located in ganglia outside of the central nervous system. The secondary neuron cell bodies (sensory nuclei) lie in the brainstem and project to the thalamus. From the thalamus the tertiary neuron projects to the sensory cortex. The sensory loss resulting from a cranial nerve injury depends on the lesion location. Peripheral nerve lesions result in a loss of all sensations supplied by that nerve, whereas central nerve injury to the sensory pathway depends on the part

injured. Damage in the thalamus causes contralateral patchy hemianesthesia and hemianalgesia.

**Somatic and Branchial Motor Pathways** The cranial nerves carrying motor functions are: III, IV, V, VI, VII, IX, X, XI, XII. Two neurons, the upper and lower motor neurons, compose the cranial nerve motor pathways. The upper motor neuron originates in the cerebral cortex and projects to the corticobulbar tract for synapse with the lower motor neuron. Most project bilaterally to contact lower motor neurons on both sides. Lesions to upper motor lesions are evidenced by paresis/paralysis, increased muscle tone, and hyperreflexia. The cell body of lower motor neurons reside in the brainstem and project peripherally. Lower motor neuron lesions cause paresis/paralysis, loss of muscle tone and muscle stretch reflexes, rapid atrophy, and fasciculations.

**Visceral Motor Pathways** The cranial nerves that perform parasympathetic efferent functions include: III, VII, IX, and X. Three neurons compose the visceral motor

**TABLE 30-2**  
*Components of Cranial Nerves*

MODALITY	CRANIAL NERVES	FUNCTION
General sensory	V, VII, IX, X	Touch, pain, temperature, pressure, vibration, proprioception
Visceral sensory	IX, X	Sensory input (except pain) from viscera (carotid body and sinus, pharynx, larynx, thoracic, abdominal viscera)
Special sensory	I, II, VII, VIII, IX	Smell, vision, taste, hearing, balance
Somatic motor	III, IV, VI, XII	Motor function of muscles developed from the somites (extraocular eye muscles and tongue muscles except palatoglossus)
Branchial motor	V, VII, IX, X, XI	Motor function of muscles that develop from the branchial arches (muscles of mastication, tensors tympani, veli palatine, facial expression, stylopharyngeus, pharynx, sternomastoid, and trapezius)
Visceral motor	III, VII, IX, X	Motor function of viscera, including glands and smooth muscle (ciliary and constrictor pupillae muscles; lacrimal, submandibular, and sublingual glands; oral and nasal mucosa; parotid gland; carotid body vasculature; smooth muscles of pharynx, larynx, thoracic and abdominal viscera; cardiac muscle)

pathways to regulate smooth muscle, cardiac muscle, and secretory cells: first-order, second-order, and third-order neurons. The first order neurons originate from the hypothalamus and higher centers and project to parasympathetic nuclei in the brainstem. From the nuclei the second-order neurons project to ganglia that lie out of the central nervous system. The third-order neurons in turn project peripherally to their targets.

### OLFACTORY NERVE (CRANIAL NERVE I)

Cranial nerve I provides the special sensory function of smell. The central axons of the bipolar olfactory neurons pass through the cribriform plate of the ethmoid bone, synapsing in the olfactory bulbs to relay sensations of smell to the brain. From here projections travel to the entorhinal cortex, hypothalamus, and the dorsal medial thalamic nucleus and then to the orbitofrontal cortex.

Cranial nerve I lesions may result in alteration of smell. Olfactory nerve injury may also alter the sense of taste because flavor perception results from a combination of smell, taste, and stored memories. Altered smell and taste may impact safety, appetite/weight control, confusion, behavior, daily activities, avocational and vocational pursuits.

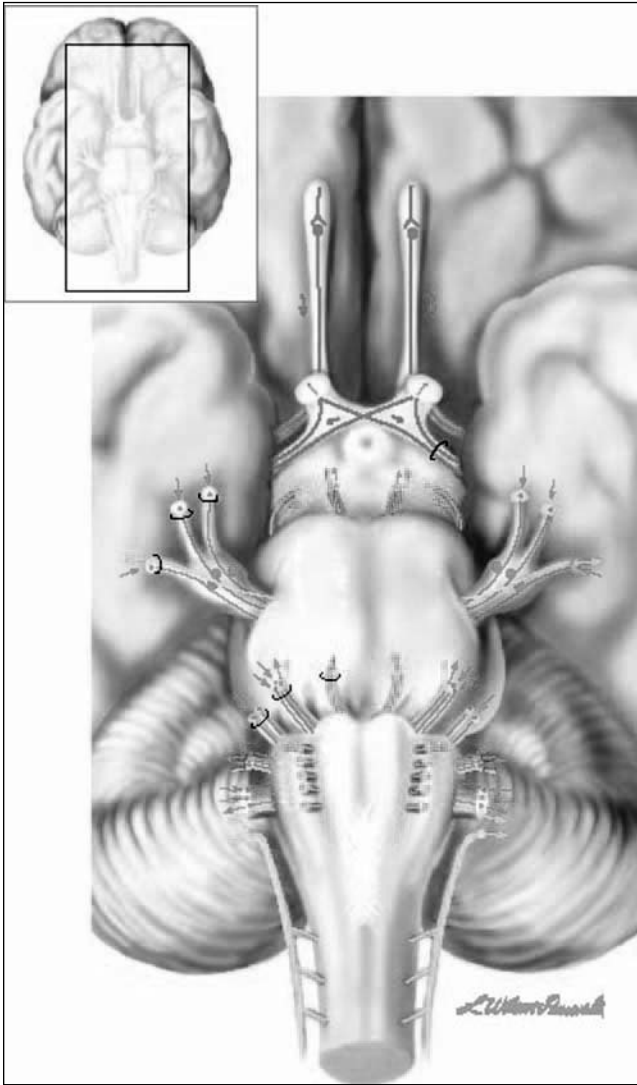
The following are terms used to describe the nature and extent of the altered olfactory sensation:

- Dysnosmia = impaired sense of smell.
- Anosmia = complete loss of smell.
- Hyposmia = partial loss of smell.
- Parosmia = sensation of smell in the absence of stimulus.

- Cacosmia = awareness of a disagreeable or unusually offensive odor that does not exist; may be part of an aura prior to seizure onset.

As many as 2 million people in the United States experience some type of olfactory dysfunction, causes of which include head trauma, upper respiratory infections, tumors of the anterior cranial fossa, and exposure to toxic chemicals or infections. It is difficult to estimate the true incidence of olfactory nerve injury in association with TBI due to the inability to examine cranial nerve I function in the unresponsive patient, and also the inconsistent seeking of medical attention after mild TBI. Olfactory nerve injury is reported to occur in 7% of all patients with TBI (8–11). The incidence is higher following moderate and severe TBI than mild TBI. Costanzo and Becker (12) report 19.4% with moderate TBI and 24.5% with severe. Injury to the olfactory nerve is the only cranial nerve commonly associated with mild TBI. This is because the fine nerve filaments of the olfactory nerve are particularly at risk for injury, even in mild TBI, as the fibers run through the cribriform plate of the ethmoid bone to reach the olfactory bulb. There should be a high index of suspicion for olfactory nerve injury in the following cases: cerebral spinal fluid rhinorrhea, frontal and occipital blows, frontal vault fractures. It is reported that 40% of those with CSF rhinorrhea after TBI experience anosmia.

Cranial nerve I injury may occur from damage to the olfactory nerves in the nasal mucosa, damage to the nerves as they cross the cribriform plate, or intracranial lesions affecting the olfactory bulbs. The olfactory filaments are particularly vulnerable to injury, as they may be sheared during the rotation of the brain or injured by cribriform plate fractures. The olfactory bulbs may be



**FIGURE 30-1**

Basal view cranial nerves exiting the brain and brainstem. The components of the cranial nerves are indicated by color: aqua = general sensory; purple = visceral sensory; green = special sensory; pink = somatic motor; yellow = branchial motor; blue = visceral motor. (see color plate)

compressed by hemorrhage, edema, contusion, or abrasion by the cribriform plate. Olfactory structures also can be injured during craniotomies involving the anterior cranial base or from subarachnoid hemorrhage, which may disrupt the fine fibers of the olfactory nerve. Delayed onset of olfactory nerve dysfunction may be the consequence of scarring or gliosis of the tissues in the cribriform plate. Other causes of olfactory sensory abnormality should also be considered, such as nasal obstruction, injury to the nasal passages, acute viral respiratory infections, rhinitis sicca, allergic sinusitis, chronic polyposis, depression, medications, and seizures. Partial complex

epilepsy with a mesial temporal focus classically includes an aura of foul-smelling odors that occur before seizure onset. Olfactory hallucinations from uncinate fits do not imply actual olfactory nerve involvement. Paranasal sinus endoscopy may lead to violation of the cribriform plate with associated olfactory nerve injury, and also potential infectious complications.

Report of impaired smell may be the first signal of olfactory nerve injury. Because olfactory nerve function is not often evaluated in an emergency situation, the dysfunction may not be detected until weeks after the injury when the patient complains of changes in taste or smell. To examine cranial nerve I function, first evaluate the patency of both nasal passages. Then, determine if the person can detect odor in each nostril by testing with a familiar substance and an empty bottle. Stimulants such as organic solvents, camphor, peppermint, or ammonia should be avoided as they may also stimulate cranial nerve V (13). Next smell discrimination can be tested with the patient choosing between a series of common odors, such as coffee, lemon, and soap. Providing choices is a helpful way of limiting the influence of word finding problems on testing. Several different scratch and sniff cards are available to make testing more convenient. The University of Pennsylvania Smell Identification Test (UPSIT) is one useful tool, consisting of 40 items which evaluate olfactory and trigeminal nerve function in the nasal cavity. Central hyposmia may manifest as abnormalities in odor recognition rather than odor detection.

Olfactory encephalography establishes the presence of alpha rhythm, and its disappearance with odor perception. Ethmoid tomography may be used to determine if a basal skull fracture is present. Positron emission tomography (PET) and functional MRI are promising modalities to assist in making the diagnosis of different types of hyposmia (central vs peripheral), as well as in delineation of the role of limbic structures as sites of odor recognition, memory, and integration of multisensory inputs. Thorough evaluation of patients who have anosmia includes imaging of the anterior cranial structures. Patients experiencing parosmia should be evaluated for seizure activity on electroencephalography.

Unfortunately, there are no established effective treatments for this condition (1), while nontraumatic causes and seizure may be amenable to treatment. Early recovery may occur due to resolution of edema or pressure; while later recovery is contributable to neurofibril regrowth and central adaptation (14). Many regain the sense of smell within 2 years, but for some this remains a permanent problem. Costanzo & Becker (12) observed 33% recovery, 27% worsening, and 40% no change. Although it is a generally annoying development, parosmia may be the first evidence of functional return. When recovery occurs, it is usually noticed within the first 6 months and complete by 12 months post-injury (13).

However, late recoveries, up to 5 years, have been reported (8). For safety purposes, individuals with altered sensation should be aware of potential risks associated with the lack of smell (eg, inability to detect dangers such as smoke, spoiled foods, toxins), reminded to install smoke alarms on all floors of their home.

### OPTIC NERVE (CRANIAL NERVE II)

The optic nerve, a fiber tract of the brain containing one million axons, provides the special sense of sight. This nerve receives its input from the rods and cones (first order neurons) which pass the signal to the ganglion cell layer of the retina (secondary sensory neurons). The long axons of the ganglion cells penetrate the lamina cribrosa as the optic nerve, which passes posteriorly through the optic canal. At the optic chiasm, where fibers from the nasal halves of the retina cross, the optic tract is formed, containing fibers from the ipsilateral halves of the retina. The optic tract continues posteriorly to the lateral geniculate bodies, where a third synaptic relay occurs. At this point, a small number of axons leave the optic tract and project to the pretectal midbrain to form the afferent loop of the Edinger-Westphal nucleus. From the lateral geniculate body, the optic tract continues posteriorly as the optic radiations, which project to the occipital lobe. Throughout their projection to the occipital lobe, the neurons maintain a highly topographic orientation of the retinal image.

Optic nerve injury occurs in up to 5% of patients with TBI (9). Optic nerve palsy may occur with injury to the globe, causing damage to the intraorbital portion of the nerve within the optic canal (15). In the orbit, the nerve is redundant and cushioned by fat. It is, therefore, not liable to indirect injury. However, the nerve is strongly tethered to bone intermittently throughout the canal. It is therefore subject to shearing forces as the brain and orbital contents are free to move, while the nerve is not (16). Injury to the optic nerve occurs most frequently in the intracanalicular portion of the nerve (17). Injury to the intracranial portion is less common.

Injury to the optic nerve typically occurs in one of two ways: 1) primary lesions causing hemorrhages in the nerve, dura and sheath spaces, tears in the nerve or chiasm, and, rarely, contusion necrosis; or, 2) secondary lesions from circulatory events subsequent to the initial injury causing edematous swelling of the nerve, necrosis from circulatory failure or local compression, and infarction related to vascular obstruction. Because the optic nerve is a direct extension of the brain, any injury to the optic nerve axons which do not regenerate is permanent.

Immediate monocular blindness occurs with great frequency in optic nerve injuries, especially in the intracanalicular portion of the nerve. Monocular blindness may be partial, and the extent of partial blindness should

be documented immediately and followed closely for deterioration. The treatment of traumatic optic neuropathy is controversial. Although some studies have shown that steroids and/or optic canal decompression to be of benefit (18–20), other studies have shown that irrespective of timing post injury, neither treatment improved visual outcome (21, 22). Complete monocular blindness with preservation of normal pupillary reflexes is usually a sign of malingering or other types of functional (non-organic) disorders.

Visual field defects are due to injury to the optic nerve or its tracts posterior to the bulbar portion. These defects are quadrantanopsias or hemianopsias of varying degrees. When such defects are due to causes other than direct pressure from a mass lesion, surgical intervention is rarely helpful. Some visual field deficits may be helped by special optics that allow the patient to “see” in the affected field (15, 23). Careful evaluation by a neuro-ophthalmologist or neuro-optometrist is warranted, and training in the use of such lenses is often necessary. Visual training may improve the visual spatial disorders for those with visual neglect (24). It is also important for the clinician to recognize non-physiologic visual field deficits.

Non-nerve-related injury also may affect visual function. Trauma to the cornea may cause visual blurring and scotomata. Visual blurring may be caused by vitreous tears, traumatically induced cataracts, retinal hemorrhage, or retinal detachment. Injury to the cornea or contents of the anterior chamber (including the lens) may cause monocular diplopia (25). If eyeglasses are of no benefit, surgery may be necessary to correct blurring caused by either corneal or lens problems. Visual blurring also may be caused by Torsion's syndrome (intraocular hemorrhage). The hemorrhage may resorb spontaneously over time or may require surgical removal for complete restoration of vision. The potential presence of occipital seizures should also be considered (26).

Examination includes testing visual acuity, visual fields, pupillary reactivity, and direct visualization by ophthalmoscope. These tests are reviewed briefly:

*Pupillary Reactivity to Light* Light is shown into each eye and pupillary constriction (or lack of response) observed. It is also helpful to test for an afferent pupillary defect using the swing eye-to-eye test. If there is an afferent lesion involving the optic nerve, light shone into the affected eye fails to produce a response in either eye (contrast that with an efferent defect as described with cranial nerve III injury in the following section). This test may be difficult to assess due to altered level of consciousness.

*Vision Acuity* This can be performed by testing the ability to read a visual acuity card or newsprint. Unfortunately, this is often unable to be performed in patients who are minimally responsive, confused, or aphasic.

Saccadic responses to optokinetic stimuli may be checked to provide evidence of residual visual acuity function. The presence of an accommodation reflex can also provide evidence of visual fixation. Visual-evoked potentials may also help establish the integrity of the optic nerve and its cortical pathways.

*Visual Fields* This entails asking the person to count fingers or identify a small object along the periphery of the vision. Each eye should be tested separately. Confrontation using a red-colored object is preferred. Evidence of visual inattention may be detected using a test of double, simultaneous extinction by presenting the test stimulus to bilateral visual fields at the same time. Tangent screen testing can provide visual field maps of deficits. Deficits may not be detected if the person is not able to fixate.

*Direct Visualization by Ophthalmoscope* This may be helpful in identifying papilloedema (a hallmark of increased intracranial pressure), anterior chamber hemorrhage, and retinal detachment.

### OCULOMOTOR NERVE (CRANIAL NERVE III)

The oculomotor nerve provides somatic motor and visceral motor functions. The nucleus of the oculomotor nerve arises in the paramedian midbrain ventral to the aqueduct of Sylvius near the superior colliculus. Mainly uncrossed fibers course anteriorly through the red nucleus and inner side of the substantia nigra, emerging on the medial side of the cerebral peduncles near the pontomedullary junction at the midline, penetrating the dura at the cavernous sinus. It travels along the lateral wall of the cavernous sinus, adjacent to the trochlear nerve, and superior to the abducens. Parasympathetic fibers from the Edinger-Westphal nucleus, which lies superior and dorsal to the oculomotor nucleus, course in close proximity to the oculomotor nerve through the cavernous sinus. The oculomotor nerve emerges through the superior orbital fissure to innervate the internal, superior and inferior rectus muscles, the inferior oblique muscle, and levator palpebrae muscle. The parasympathetic nerve fibers that travel with the oculomotor nerve innervate the sphincter muscle of the iris and to the ciliary muscle, which controls the shape of the lens during accommodation.

A palsy of this nerve can be caused by brain disorders (such as a head injury, tumor, or an aneurysm in an artery supplying the brain) or by diabetes. Injury may occur along its course: at the orbit, cavernous sinus, or an intracranial locus. This nerve is often injured at the point it exits through the dura, or from compression caused by uncal herniation due to increased intracranial pressure.

Isolated oculomotor nerve palsies due solely to TBI are not unusual, occurring in 17% of patients in one

study (27). Another study showed that persons with complete oculomotor palsy have a high incidence of traumatic subarachnoid hemorrhage (71%) or skull fractures (57%) (28). An orbital blowout fracture may produce clinical findings suggesting an oculomotor palsy; however, the simultaneous finding of infraorbital numbness argues against the diagnosis of an oculomotor nerve palsy (8).

Oculomotor nerve palsy causes a characteristic clinical picture: Divergent strabismus, since the eye is turned out by the intact lateral rectus muscle and slightly depressed by the intact superior oblique muscle. The eye may only be moved laterally. The affected eye turns outward when the unaffected eye looks straight ahead, producing double vision. The affected eye can move only to the middle when looking inward and cannot look upward and downward. There is ptosis of the eyelid, absent accommodation and in cases of complete palsy, a dilated and fixed ipsilateral pupil.

Examination involves tracking an object in the six cardinal positions, convergence on near targets, pursuit movements, saccades, pupillary reaction, and eyelid elevation. Clinical testing of oculomotor function in the conscious patient is not difficult. The examiner observes difficulty in moving the eye inward, or upward and downward, with preserved outward movement suggesting third nerve dysfunction (often with pupillary dilatation and ptosis).

In the unconscious patient, oculomotor testing is not possible, and thus, information is gathered during the performance of such tests as the doll's eye maneuver and pupillary light testing. Such tests must be performed serially, especially in the acutely injured patient, to ensure that an expanding lesion, uncal herniation, and/or hemorrhage is not overlooked. A blown pupil serves as a warning sign of herniation because of the nerves location medial to the temporal lobe at the edge of the tentorium. Dilation and fixation of both pupils indicates deep coma and possibly brain death.

Each eye is tested separately for pupillary reaction to light. With an efferent defect involving CN III, light shone into either eye fails to produce a response in the affected eye while light shone in the affected eye produces constriction of the opposite pupil. Pupillary dilation on one side is characteristic of cranial nerve III palsy, and is commonly accompanied by ptosis and lateral eye deviation (due to unopposed abducens's function). The swinging flashlight test (moving light rapidly from one eye to the next) may be helpful. The normal response to this test is constriction in the illuminated eye. A Marcus Gunn sign is present when there is dilation of the pupil of the abnormal eye after light is shone briefly into it.

The diagnosis is based on the results of neurologic examination as described above and computed tomography (CT) or magnetic resonance imaging (MRI). A spinal tap (lumbar puncture) is performed only if hemorrhage is

suspected and CT does not detect blood. Cerebral angiography is performed when a hemorrhage due to an aneurysm is suspected or when the pupil is affected but no head injury has occurred.

Return of function may begin within 2–3 months of injury, but generally remains incomplete. The chances for complete recovery are poor (28), with 40% reported to experience complete recovery (25). However, the majority fortunately experience functional recovery, which generally occurs within 6–12 months of injury.

Occlusive therapy (patching) will resolve the diplopia while the patch is on, but produces no long-term effects. Pleoptics (eye exercises) also have not been proven to be very effective (29). Strabismus surgery should not be undertaken until maximum visual acuity has been restored. Surgery should be delayed 6–9 months post injury, as one-third of patients will recover spontaneously (30). The procedure is empirical and consistent results cannot be guaranteed. Nevertheless, one large study showed successful alignment in 81% of adults who underwent strabismus surgery (31). This correction only improves the cosmetic deformity, however, and does nothing to improve the underlying cause.

#### TROCHLEAR NERVE (CRANIAL NERVE IV)

The trochlear nerve is the smallest of all the cranial nerves. It is somatic motor and innervates only one muscle, the superior oblique muscle. The trochlear nucleus is located in the lower midbrain and projects dorsally to cross the midline and eventually emerges from the dorsal aspect of the midbrain immediately caudal to the inferior colliculus. The trochlear nerve then traverses the lateral aspect of the cavernous sinus and enters the orbit through superior orbital fissure to innervate the *contralateral* superior oblique muscle. Injury of the trochlear nerve may result from trauma, ischemia, infarction, hemorrhage, aneurysm, cavernous sinus thrombosis, inflammation, meningitis, or tumor. TBI is the most common cause. The trochlear nerve is particularly liable to traumatic injury in that it has the longest course of any cranial nerve within the skull. Trochlear nerve injury is reported to occur in 0.2–1.4% of individuals with TBI (25).

Usually, the diagnosis is suspected in a person who, after a head injury, complains of vertical diplopia and cannot turn the affected eye inward and downward. The affected eye is typically observed to be rotated outward. The individual may also have a compensatory head tilt away from the affected side. In this position, unaffected muscles are employed and the vertical diplopia can often be eliminated. The double vision is commonly precipitated when walking down stairs.

What causes the vertical diplopia? With the superior oblique muscle paralyzed on one side, the antagonist

inferior oblique extorts and slightly elevates the involved eye. Consequently, the visual fields are projected onto different areas of the right and left retinæ resulting in the perception of two different images.

The superior oblique muscle performs two major functions: intorsion and downward gaze. Intorsion is difficult to detect on examination. Watching for movement of the conjunctival vessel may prove useful in this effort. Downward gaze is easier to detect. Thus, cranial nerve IV is generally tested by having the person adduct the involved eye and attempt to gaze downward. Individuals with trochlear nerve palsy are unable to look downward when the eye is adducted. Adduction of the eye prior to testing downward gaze is important because movement of the superior oblique muscle depends on the starting position of the eye.

Further examination may be pursued with CT scan or MRI imaging. Treatment depends on the cause of the palsy. Eye exercises may help. Sometimes surgery is necessary to eliminate double vision.

#### TRIGEMINAL NERVE (CRANIAL NERVE V)

The trigeminal nerve provides general sensory and branchial motor modalities. The nerve arises from the ventrolateral pons with a large sensory and small motor root. The two roots extend forward to the tip of the petrous bone, where the sensory portion merges with the gasserian (semilunar) ganglion and then forms the three divisions of the trigeminal nerve. The motor portion travels along the inferior aspect of the ganglion and becomes part of the mandibular division.

The motor fibers exit through the foramen ovale to innervate the muscles of mastication: the masseter, temporalis, and medial and lateral pterygoid muscles. The fibers also innervate several smaller muscles: the tensor tympani and tensor veli palatini via the otic ganglion, and the mylohyoid and anterior belly of the digastric via the mylohyoid nerve.

The ophthalmic division (V-1) exits through the cavernous sinus and then the superior orbital fissure to supply sensation from the forehead, conjunctiva and cornea, as well as the mucosa of the nose, frontal, sphenoid and ethmoid sinuses, and the lacrimal duct. The maxillary division (V-2) also travels through the cavernous sinus and exits the foramen rotundum to supply sensation from the skin of the mid-face, the mucosa of the anterior nasopharynx, the upper portion of the hard and soft palate, the gums of the upper jaw and the upper teeth. The sensory portion of the mandibular division (V-3) supplies sensation from the lower face, the mucosa of the lower jaw, floor of the mouth, lower teeth and gum. It supplies general sensation (but not taste) from the anterior two-thirds of the tongue.



The incidence of trigeminal nerve injury from TBI is 1.4–2% (8). The supraorbital nerve, from V-1 and the infraorbital nerve, from V-2 can be injured exiting the skull as the result of direct trauma such as blow out fractures of the orbit. Such injuries tend to occur in motor vehicle accidents, unprotected falls, golfing and baseball injuries. The peripheral branches can also be injured by a superficial blow to the face. Numbness typically follows the distribution of the nerve.

The roots and/or the gasserian ganglion may be damaged in transverse skull fractures (32), but are rare in blunt head trauma (8). Penetrating wounds involving the gasserian ganglion are also rare but may cause severe dysesthesias and trigeminal neuralgia-type pain.

Clinical testing of the trigeminal nerve involves testing of all three divisions for sensation along all of the peripheral pathways. The examiner should look for sensory sparing at the angle of the jaw which is supplied by the upper cervical roots. Testing of corneal sensation involves a crossed reflex, and involves a motor response from the facial nerve. Thus, touching one cornea lightly with a wisp of cotton normally evokes a prompt closure of both eyelids. The masseters are amongst the most powerful muscles in the body, and subtle weakness may be difficult to detect. Pterygoid weakness is easier to detect, and the examiner may note jaw deviation toward the affected muscles on jaw opening.

Decreased corneal sensation may lead to corneal abrasions and drying as indicated by marked scleral injection. Treatment includes frequent eye irrigation and use of a lubricating gel with patching of the affected eye, especially at night. If irritation continues, lateral or complete tarsorrhaphy becomes the treatment of choice to avoid corneal ulceration and the development of corneal opacities.

Although injuries to the gasserian ganglion causing dysesthetic pain are rare, as with any peripheral nerve, stretch injuries tend to damage the nerves at fixed attachments at points of sharp angulation (8). Patients with trigeminal injuries may therefore complain of dysesthesias and symptoms of trigeminal neuralgia. Patients may respond to various anticonvulsants including: carbamazepine, gabapentin, lamotrigine, zonisamide, oxcarbazepine and levetiracetam (33).

### ABDUCENS NERVE (CRANIAL NERVE VI)

The abducens nerve is somatic motor. The nerve originates at the abducens nucleus in the pons; exits the ventral pons near the midline at the pontomedullary junction; pierces the dura lateral to the dorsum sellae of the sphenoid bone; continues forward between the dura and the petrous temporal bone; takes a deep right angle turn; traverses the cavernous sinus and enters the orbit through

superior orbital fissure to innervate the lateral rectus muscle. Within the cavernous sinus the 6th nerve is situated lateral to the internal carotid artery and medial to cranial nerves III, IV, V<sub>1</sub> and V<sub>2</sub>. The cranial nerves III, IV, V<sub>1</sub> and V<sub>2</sub> travel through the dural wall, while the 6th nerve does not travel through the dura but is free within the cavernous sinus. Cranial nerve VI palsies are the most commonly reported ocular motor palsies, owing to its long intracranial course (34). This nerve has the longest intracranial course of all the cranial nerves.

Abducens nerve palsy may result from TBI, tumor, diabetes, hypertension, multiple sclerosis, meningitis, blockage of an artery supplying the nerve, aneurysm, surgery, increased pressure within the skull, orbit fractures, hydrocephalus/shunt malfunction. Injury to the Abducens's nerve in association with TBI is reported to occur in 0.4–4.1% (25).

Cranial nerve VI is often associated with injury to other cranial nerves depending on where along its course the abducens nerve is injured. Injury at the abducens nucleus is invariably associated with ipsilateral fascial nerve palsy as fascicles of fascial nerve loops around the sixth nerve nucleus. Cranial nerves III, IV, V<sub>1</sub> and V<sub>2</sub> may also be damaged when the injury occurs within the cavernous sinus due to their close proximity. When injured as the nerve passes through the superior orbital fissure, cranial nerves III, IV, and V<sub>1</sub> may be affected as they also pass through the fissure.

The lateral rectus muscle serves to move the eye laterally away from the midline (abduction). The affected eye cannot fully turn outward and may be turned inward when the person looks straight ahead. Double vision results when the person looks toward the side of the affected eye. Coordinated movements of the medial and lateral rectus muscles are required for horizontal movements. If both eyes cannot align on the same target the visual fields will be projected to different areas of the right and left retinae, resulting in the perception of two images.

These patients have an esotropia that is worsened by lateral gaze, and will often turn their heads laterally toward the paretic side to compensate. To test the abducens nerve function specifically, the patient is instructed to move the eyes through the full extent of the horizontal plane while the examiner looks for deficiency in lateral gaze.

Usually, doctors can easily identify an abducens nerve palsy, but the cause is less obvious. In the case of TBI, the cause is often apparent, but not necessarily the location. Depending on the history and presentation further work up may be needed. CT scan or MRI may be warranted to exclude tumors. A spinal tap (lumbar puncture) may be useful if meningitis is suspected. Injury to the nucleus of the nerve causes complete lack of ipsilateral gaze; injury to the nerve after it comes off the brainstem results in inability to look to the side.

Treatment depends on the cause of the palsy. When the cause is treated, the palsy usually resolves. Abducens nerve palsy following TBI generally resolves over time.

### FACIAL NERVE (CRANIAL NERVE VII)

Four modalities are carried by the facial nerve: general sensory (tactile sensation to parts of the external ear, auditory canal, and external tympanic membrane), special sensory (taste sensation to anterior two-thirds of the tongue), branchial motor (muscles of facial expression), and visceral motor (lacrimal glands and mucous membranes of mouth and nose; submandibular and sublingual salivary glands). The sensory components originate in the geniculate ganglion, the branchial motor in the main motor nucleus (pons), and the visceral motor in the superior salivatory nucleus (pons). The facial nerve exits the lower pons laterally and passes through the internal auditory meatus into the middle ear (where the chorda tympani branch arises to carry taste fibers); then enters the facial canal and exits the cranium through the stylomastoid foramen. In the parotid gland the facial nerve divides into its terminal branches.

The main function of each of the two seventh cranial nerves is ipsilateral facial movement including forehead wrinkle, eyelid closure, and movement of half of the face. A message is sent from the motor strip of the cerebral cortex crossing over to stimulate the contralateral seventh cranial nerve.

Injury to the facial nerve is the second most common, one-third as common as olfactory nerve palsy (1). Facial nerve injury most commonly occurs within its passage through the temporal bone, though it may occur at any point (13). Facial nerve injury due to TBI is most commonly peripheral, in association with temporal bone fractures. Temporal bone fractures are most commonly longitudinal accounting for 90% of all temporal bone fractures (14). Transverse fractures of the petrous bone result in immediate and complete CN VII paralysis in 30 to 50% of cases due to tearing of the nerve (13, 14). The facial nerve and vestibulocochlear nerve (CN VIII) course through the petrous bone in close proximity, and thus transverse petrous bone fractures may injure one or both of these nerves. Fractures near the internal auditory meatus usually involve both nerves resulting in ipsilateral facial weakness (i.e., the forehead musculature is involved as well as the face), ageusia in the anterior two-thirds of the tongue, and ipsilateral deafness. Temporal bone fractures further along its course may result in ipsilateral facial weakness (1).

Longitudinal fracture may result in a delay of CN VII paralysis from 2 to 3 days and up to 2 weeks. Delayed facial weakness, especially in patients with hemotympanum, is indicative of facial nerve swelling in the facial

canal. In this setting, corticosteroids should be initiated, otolaryngology consulted, and facial nerve decompression considered (1). The nerve is usually intact, and typically recovers within 6–8 weeks (13, 14).

Facial nerve palsy may occur from injury anywhere along its course from the cortex to the innervation site. Forehead wrinkle is the one clinical feature that can differentiate the cause of facial weakness. Owing to the bilateral innervation of the upper face by the two cerebral hemispheres, upper motor neuron lesions (lesions above the level of the motor nucleus of cranial nerve VII) only cause contralateral paralysis of the face below the eyes. This occurs because the part of the nucleus that innervates the frontalis and orbicularis muscles continues to receive input from the ipsilateral hemisphere, allowing these muscles to continue functioning. On the other hand, lower motor neuron VII lesions (damage to the facial nucleus or its axons along its course after leaving the nucleus) cause ipsilateral paralysis of the entire face on one side with flattening of the forehead and inability to close the eye. Pontine lesions involving the facial nucleus cause complete ipsilateral facial paralysis along with contralateral hemiparesis (resulting from damage to the descending corticospinal fibers from the motor cortex before crossing over in the medulla), and are often accompanied by lateral rectus muscle paralysis (due to proximity of abducens nucleus to the facial nucleus).

Lesions within the fallopian canal may be localized to one of the three major segments (mastoid, tympanic, and labyrinthine) based on the presentation. Loss of taste on the ipsilateral anterior two-thirds of the tongue indicates damage of the mastoid segment (which branches into the chorda tympani). Injury to the tympanic segment which serves the stapedius muscle to dampen sound waves may cause hyperacusis (sounds appear excessively loud) and loss of the stapedius reflex, as well as loss of ipsilateral taste. Impaired ipsilateral tear production (in addition to the above findings) indicates damage to the labyrinthine segment from which the greater superficial petrosal nerve originates.

Comprehensive examination of the facial nerve involves testing the five main functions of this nerve: facial expression, taste, external ear sensation, stapedius muscle function and lacrimal and salivary gland function. First, facial expression in conversation should be observed, followed by requesting performance of specific facial actions: wrinkle forehead by raising eyebrows (frontalis), close eyes tightly (orbicularis oris), press lips firmly together (buccinator and orbicularis oris), smile, and clench jaw (platysma). An enlarged palpebral fissure may be a subtle sign of facial nerve injury. Taste may be tested by using a cotton swab moistened in a sugary or salty solution. The cotton is applied to one side of the protruded tongue, taste identified, cotton applied to other side to test for side-to-side differences; mouth rinsed with

water; test repeated with the other solution. This test may be facilitated by using pre-written choices of sweet, sour, bitter, salty to which the person may point. Pain and light touch sensation is tested at the small strip of skin supplied by the facial nerve at the posteriomedial surface of the auricle, although abnormality is rarely detectable. Stapedius muscle function may be tested by having the person compare the loudness of sudden clapping behind each ear. Lacrimal and salivatory function may be assessed by asking about dry eyes, dry mouth and need for drinking water to swallow food. Lacrimal function may be formally tested using the Schirmer's test where a 5 mm by 25 mm piece of filter paper is inserted into the lower conjunctival sac for 5 minutes with less than 10 mm moisture indicating abnormal function. Because of the close proximity to cranial nerve VIII, balance and hearing should also be assessed when cranial nerve VII is found to be damaged.

Electromyography and nerve conduction studies may be helpful in providing prognostic information. In cases of complete facial nerve disruption rehabilitative surgical techniques may be helpful, such as microsurgical cranial nerve XII crossover to the cranial nerve VII. Nerve-muscle pedicle grafts from the contralateral side may offer more rapid return of nerve function without compromising neck function (35).

Misguided nerve regeneration of the salivary and lacrimal fibers may result in "crocodile tears" (tearing instead of salivation upon eating).

Inadequate lid closure may result in drying of the cornea (exposure keratitis). The problem may be further compounded by accompanying loss of corneal sensation (trigeminal nerve) (13). A topical lubricant should be used frequently to protect the eye from dryness. Additional protection may be provided by taping the lid closed with eye pad, although this is not fool proof. In severe cases, tarsorrhaphy (operation to close eye lid) may be required for protection.

### VESTIBULOCOCHLEAR NERVE (CRANIAL NERVE VIII)

Cranial nerve VIII provides special sensory functions of hearing and equilibrium/balance. Disorders of the VIII nerve may result in vertigo, tinnitus, and/or deafness. The vestibular nerve originates at the vestibular ganglion and the cochlear nerve at the spiral ganglion. In the internal auditory meatus the vestibular and cochlear nerves join and enter the brainstem at the cerebellopontine angle. Because the vestibulocochlear nerve is actually two distinct nerves that course together in close proximity through the internal auditory meatus and across the cerebellopontine angle, these two nerves are usually injured simultaneously. Once synapsing at their nuclei the nerves

take different courses, and thus, are less likely to both be injured as they run more proximally. The vestibular nuclei project through the thalamus to the somatosensory cortex providing conscious awareness of head position and balance. The cochlear nerve is represented bilaterally via fibers from the ventral cochlear nuclei.

Trauma may cause sensory and conductive types of hearing loss. *Sensory hearing loss* is caused by disruption of the transmission of auditory pathway impulses. Projections from the cochlea run bilaterally. Thus, unilateral central nervous system injury alone should not cause hearing loss. *Conductive hearing loss* results from disruption of sound transmission from damage to the tympanic membrane, ossicles, or cochlea. Hearing loss associated with TBI is more commonly sensorineural than conductive (36). Sensorineural hearing loss is reported to occur with TBI at an incidence of 85%, and 71% in the absence of temporal bone fracture (36).

Vestibulocochlear nerve injury is common with temporal bone fractures. Of all temporal bone fractures, 80–90% are longitudinal and 10–20% transverse (13). The type of temporal bone fracture, transverse or longitudinal, provides a clue as to the injury and type of hearing loss that might result. *Transverse fractures*, which tend to result from frontal or occipital blow, have been reported to result in sensorineural hearing loss in 100% of cases (37). Such injury is thought not to be amenable to surgery (13). On the other hand, *longitudinal fractures* (which occur from temporal or parietal forces) tend to result in conductive hearing loss or mixed conductive and sensorineural hearing loss (37). The incidence of sensorineural or mixed hearing loss in association with longitudinal fracture is 88%. Conductive hearing loss associated with temporal bone fractures occurs due to either ossicular chain disruption or tympanic membrane tear (13). Spontaneous recovery is reported in 80% of patients with conductive hearing loss occurring with temporal bone fractures (38). When conductive hearing loss fails to recover spontaneously, surgery should be considered. Surgical repair is associated with excellent results for all types of conductive hearing loss (37). Disruption at the incudostapedial joint occurs in 82% of cases, fracture of the stapedial arch in 30%, and malleus fracture in 11% (39). In 75% of cases of ossicular chain disruption the posterior auditory wall is also fractured (13). Although, conductive hearing loss is more common with longitudinal fractures, sensorineural or mixed hearing loss may also occur with this type of injury.

Patient examination and hospital record review may reveal important findings often associated with cranial nerve VIII injury by looking for battle's sign, mastoid fracture, otorrhea, bleeding from the ear, and hemotympanum. Hemorrhage from the ear is a common sign of longitudinal temporal bone fracture. Visualization of the tympanic membrane can be helpful to reveal tears.

Cranial nerve VIII is tested through testing eye movements, postural responses, and hearing. These assessments and how they guide lesion localization are discussed in brief detail below.

Vestibular dysfunction may manifest clinically with vertigo, nystagmus, and/or ataxia. Vertigo, the sensation of the room spinning, is a specific symptom of vestibular dysfunction. When the eyes are open, patients see the environment move; and when the eyes closed, patients feel like they are turning or whirling in space. Abnormalities in vestibular testing can be associated with lesions in the vestibular apparatus of the inner ear, the vestibular portion of CN VIII, the vestibular nuclei in the brainstem, the cerebellum, or pathways in the brainstem (such as the medial longitudinal fasciculus) that connect the vestibular and oculomotor systems. It is through observations of nystagmus and responses to provocative tests that a clinician can narrow down the origin of the problem. Thus, nystagmus elicited with extraocular movement testing, cold water caloric response testing, Dix-Hallpike Maneuver, or a rotating chair test (Ba'ra'ny Test) are key diagnostic tests in the diagnosis of vestibular pathway injury. Accompanying signs and symptoms may also provide clues to distinguish peripheral and vestibular lesions. Peripheral vestibular lesions may be accompanied by ipsilateral hearing loss and tinnitus; while central lesions may be associated with motor and sensory disturbances of the limbs, dysarthria, dysphagia or diplopia, indicating additional cranial nerve injuries.

**Nystagmus** Nystagmus is the movement of the eye in response to stimulation of the vestibular labyrinth, retrocochlear pathways, or central vestibulo-ocular pathways. To test for nystagmus, the patient is asked to follow the examiner's finger with the eyes while the examiner's finger moves through horizontal and vertical gaze. There are two components to nystagmus: slow and fast. The slow component is caused by vestibular stimulation and is mediated through the three-neuron arc from the semicircular canals to the extraocular muscles. The fast component returns eyes to the resting position and requires a functioning cerebral cortex. As a result, the fast component will not be present in coma or under general anesthesia. If nystagmus is present, record the directions of the fast-phase and slow-down phases. Nystagmus is described clinically in terms of the direction of the *fast corrective* phase, not the direction of gaze. Nystagmus is a particularly important finding because it is generally not as performance dependent as balance and coordination tests. Electronystagmography (ENG) may be used to quantify the nystagmus and provide information on the suppressive potential of visual fixation. However, ENG is not required for the diagnosis and may be considerably uncomfortable for the patient to endure.

**Vertigo** The vertigo presentation and the type of nystagmus present are important as they can help differentiate

central (CNS) from peripheral (vestibular) origin. These characteristic features are described here. *Peripheral vertigo*, commonly presenting with vertigo and emesis, is usually characterized by horizontal nystagmus with a rotary component. The fast component points away from the affected side. Duration of peripheral nystagmus is generally minutes to weeks. Some of the causes of peripheral vertigo include: benign positional vertigo, labyrinthitis, vestibular neuronitis, motion sickness, Meniere's disease, peripheral vestibulopathy, acoustic neuroma, and perilymphatic fistula. *Central vertigo* may have more insidious onset and produce mild symptoms. Central nystagmus can occur in any direction, and dissociation of movements between the eyes is possible. In central nystagmus there is no relation between the direction of the nystagmus and the location of the lesion. In general, the following types of nystagmus are central in origin: vertical nystagmus, active nystagmus without vertigo, direction changing/unipositional nystagmus, gaze paretic nystagmus, nystagmus with disconjugate eye movement, and failure of fixed suppression. Vertical nystagmus is always central in location. Central nystagmus is generally longer in duration and may be present for years. Some of the processes that present with central vertigo are: dysfunction of the vestibular portion of CN VIII, upper and lower brainstem lesions, basilar artery migraines, vertebrobasilar ischemia or infarctions, multiple sclerosis, acute cerebellar lesions (hemorrhage or infarction), cerebellopontine tumors, seizures and spinocerebellar degeneration. Metabolic causes of vertigo may be appropriate to consider which include drug toxicity, hypoglycemia, and hypothyroidism. The response to provocative tests, as described below, may also help provide such distinction. Most causes of dizziness can be determined by a complete patient history and physical examination including some of the observations described here.

**Nylen-Ba'ra'ny or Dix-Hallpike Positional Testing** This test can help distinguish peripheral from central causes of vertigo. The patient sits on the examining table, rotates the head 45 degrees with one ear down, and the examiner supports the patient's head as the patient lays back with the head extending over the edge of the table. The patient is asked to keep their eyes open and report any sensations of vertigo, while the examiner looks for nystagmus. The maneuver is then performed with the opposite ear down. The position change causes maximal stimulation of the posterior semicircular canal of the ear that is down, and of the anterior semicircular canal of the ear that is up. With *peripheral lesions*, there is usually a few second delay in the onset of nystagmus and vertigo, which then fades away within approximately 1 minute. The nystagmus is horizontal or rotatory and does not change directions (just as with peripheral nystagmus described in the above paragraph). If the same

maneuver is repeated, there is often adaptation, so that the nystagmus and vertigo are briefer and less intense each time. In *central lesions*, the nystagmus and vertigo generally begin immediately, and do not adapt. Nystagmus that persists while in this position but is not present while sitting is indicative of a central vestibular lesion.

*Vestibulo-Ocular Reflex (VOR)* This is a simple test that can be performed at the bedside and is used to determine whether or not the vertigo is vestibular in origin. Through the VOR, rapid movement of the head produces an equal and opposite movement of the eyes. This test would only be performed when there is no suspicion of spinal column instability. The patient fixates on a target while the physician quickly moves the patient's head approximately 15°. When the VOR is intact, the eyes will remain focused immediately on the target after the head is thrust. If the patient must make corrective eye movement to see the target, the VOR is decreased. Corrective eye movements (saccade) with left and right head thrust indicate vestibular dysfunction on the left and right sides, respectively.

*Head-Shaking Nystagmus* This is nystagmus that appears after vigorous horizontal head shaking for about 15 seconds, at a frequency of approximately 2 Hz. Head-shaking nystagmus occurs when there are differences in the peripheral vestibular input reaching the central velocity storage mechanism of the brainstem. Thus, a positive head-shake test is suggestive of a peripheral lesion.

*Walking with Sudden Turns Test* This test produces veering toward the side of cerebellar or labyrinthine disease. To perform this test the patient should pivot on given points on the floor.

*Fucada Stepping Test* This test is performed by asking the patient to march in place with eyes closed for 50 steps at normal walking speed. The examiner makes note of distance and angle of displacement from starting to final standing point, angle of rotation, body sway, changes in head position relative to the body, position of the arms in horizontal or vertical directions. The final standing position is regarded as abnormal if there is more than 30° of body rotation or more than 50 cm of displacement from the starting point. Individuals with unilateral vestibular pathology often turn excessively. The test is not specific to vestibular dysfunction, but may provide a supportive finding taking other findings into account.

*Caloric Stimulation Testing* For individuals in a low neurologic functioning state, assessment of the vestibular system through the above tests is not possible. In such patients, caloric stimulation testing may be particularly

helpful for this purpose. This test is performed with the head of the bed placed at 30 degrees to have the horizontal semicircular canal in a vertical plane. The external auditory canal is then irrigated with 30 degree Celsius water over thirty minutes while direction of eye deviation and nystagmus are observed. With the intact vestibular system, the eyes tonically deviate to the side of cold irrigation, and then followed after an approximate 20 second latent period by nystagmus to the opposite side that generally lasts 1.5 to 2 minutes. The procedure is repeated using 44 degree Celsius water. With warm water irrigation the nystagmus is normally to the side of the irrigation. The normal nystagmus response to caloric testing follows the mnemonic COWS (Cold Opposite Warm Same). When there is dysfunction in the vestibular pathway this response may be reduced or absent.

Hearing loss can be caused by lesions in the acoustic and mechanical elements of the ear, the neural elements of the cochlea, or the acoustic nerve (CN VIII). There are three general types of deafness: conductive, sensorineural, and central. Conductive hearing loss results from a defect in the mechanism by which sound is transformed and conducted to the cochlea as occurs with disorders of the external or middle ear. Sensorineural hearing loss results from disease of the cochlea or of the cochlear division of the eighth cranial nerve. Central hearing loss is caused by lesions of the cochlear nuclei and their connections with the primary receptive areas for hearing in the temporal lobes.

After the hearing pathways enter the brainstem, they cross over at multiple levels and ascend bilaterally to the thalamus and auditory cortex. Therefore, clinically significant unilateral hearing loss is invariably caused by peripheral neural or mechanical lesions. On the other hand, the bilaterality of the CNS connections prevents unilateral central injury from causing significant hearing loss.

Hearing may be assessed at the bedside by seeing if the patient can hear the examiners fingers rubbed together outside of the auditory canal. Similarly, the patient may be asked to cover one ear while the examiner whispers in the other ear and has the patient repeat what is heard. Testing on the two sides is compared. If hearing impairment is detected the cause may be localized and differentiated as sensorineural or conductive using the Rinne and Weber's Tests.

*Rinne Test* For the Rinne Test, a 512 Hertz tuning fork is placed over the mastoid process (bone conduction) until the patient indicates that the ringing sound is no longer heard, and then the tuning fork is placed a few centimeters from the external auditory canal (air conduction). In this second position of air conduction, sound is normally conducted through the external and middle ear to the cochlea. Normally, the tone is heard better by air conduction, and

thus, with normal hearing the ringing should be heard again in the second position. Not being able to hear the sound again by air conduction implies conductive hearing loss. That is, the problem is in the external or middle ear. With conductive hearing loss, bone conduction is heard as it bypasses problems in the external or middle ear. Rinne Test findings in sensorineural hearing loss are the same as with normal hearing, air conduction is greater than bone conduction in both ears, except hearing is decreased in the affected ear.

*Weber Test* The Weber Test is performed by placing the tuning fork over the middle of the forehead transmitting sound via bone to the cochlea and bypassing the middle ear mechanism. Normally the sound is heard equally on both sides. In sensorineural hearing loss the ringing is not as loud on the affected side, while in conductive hearing loss the ringing is heard louder on the affected side. You can replicate this increase in sound on the side of conduction block by covering and uncovering one ear with the cup of your hand while humming.

Formal audiometry may be helpful to detect and quantify hearing loss, differentiate sensorineural from conductive loss, and guide treatment decisions. In the lower neurologic functioning individual with TBI, brainstem auditory evoked potentials can be used to test the intactness of the auditory pathway. This may be particularly important in helping guide therapy towards more visual stimuli in trying to elicit reactions. Hearing loss may pose significant obstacles to the patient and treatment team in rehabilitation and community integration that should be considered in the rehabilitation program.

Treatment of cranial nerve VIII injuries can best be discussed in terms of the 2 main problems of vestibular and hearing impairment. Treatment of vestibular dysfunction is based on the vestibular system's capacity to habituate to stimuli (13). To decrease the vestibular sensitivity, labyrinthine exercises are used that incorporate equilibrium and righting reflexes (40). Referral to a physical therapists knowledgeable in the diagnosis and treatment of dizziness related to TBI can be a valuable component in the management of this disorder. Medications commonly used for vestibular problems (such as meclazine or dimenhydrinate) are generally not helpful and are discouraged due to potential sedation, cognitive side effects, and prevention of central adaptation (13).

Significant unilateral hearing loss may be improved using a CROS (contralateral routing of signal) type hearing aid which transfers sound to the intact ear (13). Surgical correction is an important consideration for conductive hearing loss that fails to recover spontaneously. For the management of tinnitus, masking sound devices and biofeedback have both been successful in some cases (13) and may be worth consideration.

## GLOSSOPHARYNGEAL NERVE (CRANIAL NERVE IX)

The glossopharyngeal nerve serves general, visceral and special sensory functions, as well as branchial and visceral motor functions. This nerve exits from the jugular foramen in close proximity to the last three cranial nerves; therefore, lesions, especially traumatic ones, tend to affect some or all of those nerves. The glossopharyngeal nerve provides general cutaneous function and taste to the posterior one-third of the tongue, and sensation to the soft palate, pharynx, faucial tonsils, tragus of the ear and nasopharynx. Its tympanic branch supplies sensation to the tympanic membrane, eustachian tube and mastoid area. Chemo and baroreceptors are also carried by the glossopharyngeal nerve from the carotid body and carotid sinus. Its motor fibers innervate the stylopharyngeus muscle and, along with the vagus nerve, the pharyngeal constrictor muscles. Parasympathetic secretory and vasodilatory fibers innervate the parotid gland.

The incidence of glossopharyngeal dysfunction following trauma is 0.5-1.6% (8). Symptoms include loss of taste over the posterior one-third of the tongue, deviation of the uvula toward the contralateral side, decreased salivation and slight dysphagia. Examination includes testing oropharyngeal sensation and gag reflex. Loss of sensation to the posterior palate with a subsequent absent gag reflex may place the patient at risk for aspiration. Treatment for an isolated glossopharyngeal nerve injury is symptomatic, as the symptoms are usually minimal. However, injury to the glossopharyngeal nerve usually involves the vagus as well, and thus, may result in severe laryngeal and pharyngeal dysfunction. Treatment of such injuries is covered below.

## VAGUS (CRANIAL NERVE X)

The vagus nerve arises from the lateral medulla, leaving the skull through the jugular foramen with the glossopharyngeal and accessory nerves. It contains motor, sensory and parasympathetic fibers. The vagus nerve supplies motor fibers to all the striated muscles of the pharynx and soft palate except the tensor veli palatini and stylopharyngeus. Through the superior and recurrent laryngeal nerves, the vagus supplies all of the striated muscles of the larynx. Parasympathetic motor fibers supply the smooth muscle of the trachea, bronchi, esophagus and gastrointestinal tract, and cause gastrin release from the antral mucosa. It also sends inhibitory fibers to the heart muscle, slowing the heart rate and reducing the amplitude of the heart beat. Sensory fibers innervate the pharyngeal plexus, larynx, and thoracoabdominal viscera.

The incidence of vagal involvement in TBI is .05 to .16% (8), usually as the result of blunt trauma associated

with occipital condyle fractures. Bilateral vagal disruption is fatal.

To examine vagus nerve function test palate elevation and gag reflex. Injury to the vagus nerve, especially the superior and recurrent laryngeal nerves, may result in: paralysis of the palate with loss of the gag reflex, dysphagia, and aphonia with unilateral paralysis of the vocal fold. Alternative feeding techniques should be identified for those at risk for aspiration. Pharyngeal exercises may improve dysarthria in individuals with mild dysfunction (40). Glottic incompetence can be treated by procedures that augment vocal cord bulk, such as the injection of Teflon, Gelfoam or fat. More aggressive surgical procedures such thyroplasty and arytenoids adduction have been reported beneficial to those with high vagal lesions (41).

### SPINAL ACCESSORY (CRANIAL NERVE XI)

The spinal accessory nerve is a pure motor nerve with two parts. The cranial part (accessory vagal nerve) arises from the medulla, exits the skull via the jugular foramen, and in conjunction with the vagus nerve, supplies all the intrinsic muscles of the larynx except the cricothyroid. The spinal part (accessory spinal nerve) arises from anterior horn cells of the first through sixth cervical cord segments. The fibers form a trunk that ascends and enters the foramen magnum, where it joins the accessory vagal nerve before exiting the jugular foramen. After joining with the vagus nerve, the fibers split off to descend in the neck to supply the sternocleidomastoid muscle and the upper half of the trapezius.

Trauma, especially from missiles, is the most common cause of spinal accessory nerve dysfunction. Symptoms include the inability to turn the head to the opposite side, and ipsilateral shoulder drooping, resulting in shoulder dysfunction and pain.

Examination includes testing trapezius function on shoulder shrug, sternocleidomastoid on contralateral head turning, and flaring of the scapula. Aggressive physical therapy should be initiated as soon as possible. Surgical repair of the accessory nerve after sectioning may be possible in some patients.

### HYPOGLOSSAL (CRANIAL NERVE XII)

The hypoglossal nerve serves somatic motor function. It emerges from the medulla, and leaves the skull via the hypoglossal canal. It innervates the ipsilateral intrinsic tongue musculature as well as the hyoglossus, styloglossus, genioglossus and geniohyoid muscles. It is responsible for tongue protrusion to the opposite side.

Injury to the hypoglossal nerve causes dysarthria and dysphagia. Injury to the hypoglossal nerve alone

most often occurs with penetrating wounds to the neck and submental region. Ipsilateral atrophy and tongue fasciculations are noted on examination. Upon protrusion, the tongue deviates toward the lesion by the unopposed, contralateral muscles. With a supranuclear (central) lesion, however, the tongue will deviate opposite the lesion due to contralateral innervation of the brainstem.

Examination of hypoglossal nerve function involves noting tongue protrusion. The tongue deviates to the side of the lesion. Exercises for the treatment of dysarthria may help to improve tongue coordination and strength. Treatment of hypoglossal nerve injuries due to penetrating wounds is surgical, and the nerve tends to recover quite well.

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# 31

## Fatigue: Assessment and Treatment

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**F**atigue is a commonly reported symptom following Traumatic brain injury (TBI), yet it is both poorly understood and challenging to treat.

The word symptom is used in contradistinction to diagnosis because fatigue in general and specifically in TBI is so problematic to define and operationalize. Since TBI is a descriptive term for a heterogeneous collection of injuries to the brain that can result in physical, behavioral, cognitive or emotional dysfunction, it has been particularly vexing to determine the origin of and how to best characterize post-traumatic fatigue (PTF). As a result, the determination of its incidence has been problematic. Some attempts to quantify its incidence in TBI have placed the range between 21 and 73 % (1, 2, 3). PTF affects not only an individual's emotional well being but may also affect potential functional recovery from brain injury. Kreutzer, Seel, & Gourley (4) reported an incidence of 46% among persons in an outpatient TBI clinic and suggested that further information needs to be gathered regarding prognostication and the efficacy of treatment alternatives. However because of its multifaceted nature, the overall burden of fatigue in this population is not precisely known. However, individuals with TBI clearly suffer from fatigue with resultant diminished functioning in multiple spheres of cognition, quality of life and activities of daily living. This

functional limitation is especially problematic because the inability to sustain purposeful, goal-directed mental effort is a key requirement for independent functioning. Clinicians who attend to persons with TBI often possess few diagnostic or therapeutic resources to offer accurate assessment and treatment. Recently, however, a number of new and sophisticated neuro-imaging tools and techniques have helped to begin unraveling the underlying pathophysiology of PTF and should soon reveal more about treatment. The following discussion will review the available knowledge concerning fatigue in the TBI population. Our intent is to simultaneously educate and increase readers' interest and understanding of fatigue; to promote research in this critical area leading to productive, multi-disciplinary efforts addressing the problem of fatigue; and to facilitate the development of treatment protocols through the identification of possible fatigue generating mechanisms. Meanwhile, the state of the art approach to managing PTF is offered.

For the following discussion, TBI will be defined using the well established definition advanced by the TBI Model Systems Task Force: "damage to brain tissue caused by an external mechanical force, as evidenced by loss of consciousness, post-traumatic amnesia, skull fracture, or objective neurological findings that can be reasonably attributed to TBI on physical examination or mental status examination" (5).

## DEFINITION

Prior to embarking on a further discussion of PTF, we develop a working definition for it. It is important to recognize that no universally accepted definition or broad consensus on a conceptual framework of fatigue in general exists. Nevertheless, discussions in the fatigue literature make a distinction between *central* fatigue, which results from dysfunction of supratentorial structures involved in mentation, versus *peripheral* fatigue, which is of a more purely physical, metabolic or muscular origin. Clearly, it is the *central* type that is of greatest interest with regard to those with isolated TBI. Beyond this dichotomy, the debate over PTF or fatigue in general has moved beyond the idea of fatigue as a unitary concept and towards a belief that fatigue is multifaceted (6, 7) with components likely arising from distinct mechanisms and brain networks (8).

Lezak's reductionist, "fatigue needs no definition" (9), may be the battle cry of the lumpers in this debate; however, such a pronouncement does little to advance our understanding of this phenomenon and for the development of effective treatment strategies. On the other end of the spectrum, Chauduri and Behan (10) carefully define PTF as ". . . the failure to initiate and/or sustain attentional tasks and physical activities requiring self motivation (as opposed to external stimulation) . . ." and they lay out an elegant clinico-anatomic, pathophysiological explication of why fatigue follows acquired brain injury. Clinical experience echoes their definition in that fatigue impacts upon cognitive function (11) and the ability to perform instrumental activities of daily living.

Historically, various surrogates, markers, synonyms and clinical imitators of fatigue have been pursued in the literature, leading the casual reader astray from a purer characterization of the fatigue that follows TBI. Yet almost paradoxically, the more focused and penetrating the research on the essence of fatigue becomes, the less singular a phenomenon it appears to be. Thus, even as one measures, correlates and localizes the fundamental components of fatigue, the syndrome or symptom cannot merely be appreciated in isolation. Rather, fatigue must be appreciated in its full context, across various domains and with the understanding that the fatigue experience is not static or constant. Ultimately, the clinical picture of PTF that emerges is colored and textured by a multitude of primary and secondary, even tertiary factors that reliably engender the principle aspects of fatigue for persons with TBI. The current discussion hopes to elucidate the most likely generators of PTF and critique the current literature as well as propose an operational definition based on the most appropriate measurement tools for its assessment.

## EPIDEMIOLOGY

Currently employed methods of surveillance for disease burden due to TBI do not collect information beyond that of the total number of emergency room visits and the total number of hospitalizations. Moreover, the vast majority of TBI's are deemed *mild* and the CDC has labeled this variant the "silent epidemic" because many such cases never receive medical attention. Consequently the magnitude of the problem of fatigue among all TBI survivors or that subset "permanently disabled" is not directly known. Disappointingly even databases developed through the comprehensive Traumatic Brain Injury Model Systems are simply silent with respect to surveillance of PTF or its consequences. Thus, TBI stands as a persistent public health burden that, despite primary prevention successes, will likely continue to grow because of the increasing sophistication and effectiveness of contemporary emergency care, further resulting in a growing *prevalence* of TBI-associated problems such as fatigue. In the vast majority of studies, PTF is evaluated predominantly by self-report—in other words, subjectively. A number of investigators over the last several decades have attempted to identify the incidence or prevalence of fatigue in the TBI population, but these studies have not always been adequately controlled for such common confounds as anxiety and depression. Lezak (9) identified fatigue as one of the "subtle" sequelae of brain damage, along with distractibility and perplexity, and compared the incidence of fatigue between those patients seen in consultation, (i.e. relatively briefly), with those enrolled in detailed, longitudinal research protocols. Forty-two percent of 50 subjects reported fatigue if examined once and 60% if examined more often. Among the group in research studies ( $n = 46$ ) the reporting of fatigue reached an astounding 98%. This study exposes how a methodological flaw can seriously compromise the estimated incidence of PTF. The marked discrepancy suggests that thoroughness of assessment is essential and that without such an approach, patients are at risk for having their fatigue go unrecognized especially as TBI severity increases and with it, cognitive dysfunction such as memory and self awareness.

Middleboe (1) analyzed a cohort of 51 patients with mild TBI and noted that 21% reported fatigue one year post injury. Olver (3) studied a longer follow-up period for 254 patients at 2 years and 103 at 5 years. The majority of these patients had suffered a severe injury as reflected by a mean Glasgow Coma Score of 5.1. Fatigue was reported by 68% at two years and 73% at 5 years. Masson (12) studied a group of 231 adults five years after injury. The sample was stratified with respect to TBI severity and in addition, a lower limb injury cohort was used for comparison. Among the four groups, 30.6% of limb injured, 35.1% of mild TBI, 32.4% of moderate TBI

and 57.7% of severe TBI subjects endorsed fatigue suggesting an association between severity of brain injury and fatigue incidence. Hillier (2) examined a cohort of 67 primarily severely brain injured patients and noted a fatigue self-report rate of 37% five years post-TBI. This number may be artificially low in light of the under self-reporting noted by Lezak especially since the overwhelming majority of patients in this study were severely injured (73%) and likely to have disabling cognitive impairments. Kreutzer et al. (4) examined the epidemiology of depression in a cohort of 722 TBI outpatients on average 2.5 years after injury and with a mean duration of unconsciousness of 10 days. The self-report of fatigue in this severely injured group was 46% and fatigue was the most frequently reported problem.

From these type of epidemiological studies based on self report, PTF ranges from 2 to 98 percent (13). What remains unclear from these reports is how fatigue impacts upon mentation or on function. Limited formal neuropsychological evidence exists to elucidate the effect of PTF on cognitive performance. In addition, it is not clear what the natural history of fatigue is, or what the associations are between fatigue and a multitude of TBI-specific factors such as length of coma, duration of posttraumatic amnesia and mechanism of injury. Finally, it is unknown how the incidence and magnitude of fatigue interrelate, affect, and are affected by other common TBI sequelae.

## ASSESSMENT

To date there is no single measurement instrument that has been validated to study PTF. Nevertheless, it is important to begin the process by assessing the *impact* of PTF. Efforts at the assessment of PTF have been complicated by its multifaceted nature. Many measures that are commonly used rely on subjective reporting. Some of the more commonly employed scales used in neurological populations are the Fatigue Severity Scale (FSS) (14), Fatigue Impact Scale (FIS) (15) and the Modified Fatigue Impact Scale (MFIS). The FSS (14) is assessed by having participants rate 9 different questions rating one's fatigue from 1 (low) to 7 (high). The FSS is the average of these 9 values. The FIS (15) is a 40-item questionnaire that the person rates from 0, no problems, to 4, severe problems. These items are grouped into three separate functional categories—physical, cognitive and psychosocial. The MFIS is a 21-item derivative of the FIS that is more commonly used in the multiple sclerosis population.

In an effort to delineate both subjective and objective assessment of fatigue Lachapelle (16) evaluated thirty subjects with TBI a mean of 44.3 months after injury and compared them to an age and gender matched healthy control group. The study purported to parse fatigue into

objective and subjective components; the paradigm for objective fatigue was a continuous thumb-pressing task. Over time, normal and TBI groups demonstrated a decline in the number of repetitions per unit of time, however the difference was statistically insignificant. The subjective evaluation of fatigue was quantified by visual analogue, the FSS and FIS scales. Despite the statistical parity on the objective measure, TBI patients demonstrated significantly greater subjective fatigue scores on the FSS and FIS versus normal controls. Likewise, Walker (13) looked at the measures of quadriceps strength and physical endurance to test those complaining of PTF versus normals and found no statistical difference. Researchers trying to characterize peripheral fatigue note the significant impact upon challenging physical actions facing those with brain trauma, such as mobility, ADLs and sustaining endurance for a given task. Brain trauma often involves lesions of central pathways governing simple and complex motor function, for instance resulting in hemiplegia, spasticity, ataxia or the upper motor neuron syndrome with various well-known positive and negative signs and static and dynamic disturbances. Given the working definition of peripheral fatigue as “any reduction of maximal force output” (17), it is easily appreciated how impaired motor and sensory (modulation) centers translate into increased energy demands and reduced efficiency of ambulation, for example, quickly resulting in a fatigued individual. Thus, while we have seen above how some effort is made to distinguish *central* from *peripheral* fatigue in theory, there remains such overlap that no specific study targeting this distinction has yet been published. We are therefore left with the crude assessment tools currently available, leaving us sliding either way on a slippery slope because even purely *peripheral* fatigue must necessarily be perceived by and processed within the context of the *central* nervous system. It should thus not be surprising that so frequent a dichotomy exists between what is measured and what is perceived.

## MECHANISMS

The biological “substrate” of fatigue in normal individuals is not known. Furthermore, the study of PTF is made more difficult by the fact that in our clinical experience this symptom does not occur in isolation but rather is part of a broader array of signs and symptoms post injury. Functional neuroimaging reflects yet another level of inquiry into the morphology of the fatigued brain, attempting to correlate anatomy with task-specific activity.

### Anatomical

Given the heterogeneity and variety of lesions from TBI, a discussion of the source of fatigue should begin with a

consideration of the underlying neuroanatomy associated with known pathophysiological mechanisms. For instance, TBI may include focal or diffuse, hemorrhagic or non-hemorrhagic, coup and contrecoup, contusional, and compressive (epi- and subdural) as well as numerous secondary and clinically superimposed causes of CNS tissue damage. Because natural traumatic forces never injure the brain in exactly the same way, the various neural circuits that support optimal cognition are differentially impaired. This leads to different degrees of cognitive dysfunction from individual to individual, further permuted by the occurrence of damage within the context of each brain's unique set of premorbid strengths and weaknesses. From a strictly statistical standpoint, the generally fatigued brain may yield a potentially infinite number of specific patterns of underperformance.

The multiple structures subserving arousal are known collectively as the ascending reticular activating system (ARAS), emanating from the brainstem and represented in each of its three divisions by the following nuclei:

Medulla: raphe and reticularis ventralis (serotonergic)

Pons: parabrachialis (cholinergic), locus ceruleus (noradrenergic), reticularis pontis oralis and caudalis and the gigantocellularis

Midbrain: pedunculopontine tegmental (PPT) and laterodorsal tegmental (LDT) nucleus (cholinergic); raphe (serotonergic) and ventral tegmental area or VTA (dopaminergic)

The outputs from these structures coalesce into two pathways, the ventral and dorsal pathways of the RAS. The ventral pathway terminates in the subthalamus and posterior hypothalamus, which in turn send histaminergic fibers to a broad array of cortical end points. In addition, the ventral pathway contains a projection via the MFB to the septal nucleus and basal forebrain, which in turn send a broad array of cholinergic fibers to the cortex. The dorsal pathway projects to the interlaminar nucleus of the thalamus from which, in turn, glutaminergic tracts emerge to project across a variety of cortical and striatocortical endpoints (18).

The ARAS is a fundamental structure maintaining arousal as a prelude to alertness and bilateral injuries in the brainstem nuclei result in loss of consciousness (19). This system, however, is a part of a larger and more complex system, which maintains sensory attention and tonic arousal. When there is sufficient diffuse damage (DAI) to tracts or pathways mediating general arousal, immediate unconsciousness continues over a period of variable duration depending on the extent of damage (see Chapter 8 in this book). Therefore, a frequent and major component of TBI is a disruption in the neuro-anatomical structures maintaining arousal through shearing of

axonal connections. DAI thus results in insufficient amounts of neurotransmitters normally released by more caudal structures reaching their targets, yielding an unstable platform from which to launch desired cognitive processes and behaviors, including fundamental elements subserving cognition such as attention and processing speed.

### Basal Ganglia

In a recent review article, the investigators Chaudhuri and Behan (10) offer the hypothesis that the basal ganglia (BG) are the neuroanatomical site at which fatigue is generated following neurological injury. Specifically, they identify the disruption of two "loops", the striato-cortical fibers and the striato-thalamo-cortical fibers, as the mechanism responsible for central fatigue. Such critical pathways have been carefully delineated over the last two decades and now reveal influential and tight connections between the striatum of BG and a key component of limbic signaling, the archistriatum or amygdala. The limbic system clearly provides a route by which unconscious, spontaneous, emotionally driven motivational forces may exert influence on the motor system, thereby altering the chances that goal-directed behaviors get initiated and sustained.

In bilateral BG damage, a lack of drive, initiation and motivation is often encountered. Termed *abulia* when severe, it may be misinterpreted or overlooked altogether when more mild and is usually identified as mere apathy by rehabilitation team members. A dopaminergic pathway called the mesencephalofrontal activating system (MFAS) projects from the VTA of the midbrain to frontal regions, especially cingulate gyrus, and drives internal states towards motivated behavior. Thus, under normal circumstances, initiation and sequential performance of a task require an internally driven mechanism integrated at the level of the BG to prepare the emotive, motor and sensory apparatus responsible for the next and subsequent set of responses. Disruption of these algorithms of the sequential task processing mechanism would have the effect of not only delaying initiation, but also preventing the seamless, well-timed execution of the target task (10).

Although direct support for their theory is lacking, if it is placed within the context of the ARAS as the "substrate" for maintaining alertness, then fatigue may represent a decrease in this normal state of alertness. How this occurs is not known; however, Whyte et al. (20) have demonstrated how difficulty sustaining arousal and attention post-TBI affects cognition. They compared a cohort of 26 TBI patients with normal controls using a visual vigilance task. The results revealed "severe TBI does result in difficulties maintaining stable performance over time in an attention demanding task, independent of specific

distracting events.” While there was no formal assessment of fatigue in the TBI cohort in this study, the authors hypothesize that this inability to sustain performance reflects declining arousal or increasingly frequent lapses of attention. In a separate paper, Whyte drew a distinction between the tonic and phasic arousal. The former term is used to describe baseline alertness and wakefulness, while the latter refers to the arousal that is demonstrated in response to stimuli or as demanded by a distinct task. This runs parallel to the concept of the ARAS as not only mediating tonic activation and arousal but also playing an important role in the ability to phasically turn on cortical tissue in an efficient manner to perform upon demand.

This concept is also reflected by Heilman and Valenstein’s (21) assertion that “brain regions . . . are essentially silent unless and until activated by release of the appropriate transmitter . . .” Thus, PTF may be conceptualized as an inability not only to activate but also to efficiently sustain and recruit cortical tissue subserving cognitive tasks.

Riese et al. (22) attempted to study the impact of central (mental) fatigue on cognition. These investigators studied eight young severely injured TBI patients more than nine months post injury. All of the patients studied had suffered not only severe but also diffuse injury and in fact one inclusion criterion was “no documented focal lesions”. Fatigue was not assessed via self report. Rather, the authors assessed the ability to sustain workload via a “continuous dynamic divided attention task”. The study findings revealed no difference between control and TBI subject groups in terms of the effect of “task load” on performance but an increased amount of mental effort was required among the TBI cohort for maintaining the task. The finding of increased mental effort among the TBI cohort was corroborated through both subjective and physiological indicators of distress. It is conceivable that this increased effort may correlate with perceived fatigue.

### Neuroimaging

A recent fMRI study by Christodoulou et al. (23) examining working memory may offer one possible explanation for the findings in both the Whyte and Riese studies. This fMRI study examined the differences in cortical activation in seven controls versus nine TBI subjects while performing the mPASAT, a progressively more difficult computation task commonly used to assess working memory. Impairments in working memory among TBI subjects resulted not surprisingly in a higher incidence of error on the mPASAT test but interestingly, fMRI scanning further revealed a more regionally dispersed and more lateralized pattern of cerebral activation. In a related case report by Hillary et al. (24), the TBI participant completed the working memory task in the fMRI both pre and post treatment

with stimulant medication (methylphenidate and modafinil). Performance improvement was observed with stimulant medication, which also resulted in decreased cerebral activation on fMRI that correlated with the patient’s self-report of greater ease in performing the task.

This increased level of cortical activation for a given task likely reflects not only inefficiency in ‘phasic’ recruitment of cortical assets but also suggests that the inefficiency results in increased metabolic demands as visualized on the fMRI images. The increased amount of cortex required per task in TBI versus normal controls is accompanied by the perception of greater mental effort as well.

Therefore, informed speculation leads us to identify motor coordination centers (basal ganglia), executive and motor planning areas (frontal circuits) and internal motivational apparatus (hypothalamus and related limbic structures) as the main arbiters of fatigue-associated behavior. When one or more of these systems is affected, individuals routinely fail to complete the execution of incremental or serial tasks that demand sustained motivation and attention.

### Functional

In seeking an all-inclusive, unifying theory of the mechanism of PTF, we cannot ignore the contribution of several, clinically encountered factors. Clinicians will certainly recognize the recurring theme of one symptom or system dysfunction reflexively exacerbating another component of the index disease. For example, mood disturbances will impact upon sleep/wake cycles which, when disturbed, tend to amplify mood disorders. Pain, (frequently encountered with comorbid multi- or craniocervical trauma), puts the individual at higher risk for mood and sleep disturbance; and conversely, those with dysfunctional mood or sleep are more apt to experience magnified pain (25–27). It is easy to appreciate how these interactions pose a mounting burden that cumulatively impedes optimal cognitive function. Perhaps, at its simplest mechanistic level, PTF represents and reflects the final common pathway’s *product* of neural processing, impaired by some combination of primary damage and secondary or tertiary factors impeding cohesive, efficient and coordinated cognitive output.

### OTHER COMPONENTS OF THE FATIGUE EXPERIENCE

In addition to primary neurological injury, there are many other factors that can impact both the functional and subjective reporting of fatigue in populations other than TBI. Since they are also found in TBI, such factors can also likely impact PTF. The following sections discuss these issues.

### Psychology/Psychiatry

Depression commonly manifests as disturbances in sleep and appetite, decreased concentration, loss of interest, fatigue, and suicidal behaviors—all of which may often be found following TBI. At least two thirds of those studied describe fatigue, low energy or listlessness, making this one of the most common somatic complaints of depression (28, 29). Kreutzer (4) and Seel et al. (30) also found fatigue to be the most common symptom endorsed by depressed individuals with TBI. Statistically, depression predicts fatigue and fatigue predicts depression in the general population.

The neurobiological dysfunction in depression consistently involves 5-HT and NE systems and the limbic-hypothalamic-pituitary-adrenal (LHPA) axis (31), again demonstrating tremendous overlap with impairments following TBI (see endocrinology section below). Many attentional and cognitive deficits seen in depression are thought to be mediated by the prefrontal cortex, which receives significant NE and 5-HT input (32). Functional neuroimaging studies have recently elucidated frontal cortical-limbic pathways critical to modulation of depression and anxiety (33, 34). Given the frequency with which frontal damage occurs in TBI, one should commonly expect psychological dysfunction with its additive burden upon cognition, especially with what is known about how these internally distracting disease states interfere with cognition in those without TBI.

### Biochemical

TBI results in a cascade of events that includes biochemical and cellular derangements. The ability to make sense of these changes is limited by the complexity of neurochemical processing in the brain. At the biochemical level, it is well known that amino acid levels are altered by TBI. Aquilani et al. (35) noted that levels of tyrosine and essential amino acids are decreased after TBI and that there is a persistent decline even upon discharge from acute rehabilitation. Two especially important amino acids for CNS function are tyrosine, a precursor to brain catecholamines, and tryptophan, an essential amino acid and precursor to serotonin. The neurotransmitter serotonin has been implicated in fatigue. The relationship between TBI disruptions in neurochemistry and the sensation of fatigue is suggested by Dwyer and Browning (36) who noted that *m*-chlorophenylpiperazine (*m*-CPP), a 5HT<sub>1A</sub> agonist, induces fatigue in an animal model, and that exercise training over a prolonged period diminished the response to this agent. Bloomstrand (37) concluded that exercise-related fatigue in the CNS was correlated to 5HT because elevated levels impaired performance whereas decreased levels improved running in an animal model. One known mechanism of tryptophan regulation provides further support for its role in central fatigue, namely

that, through competitive binding for CNS transport proteins, branched-chain amino acids (BCAA) have an inverse relationship with tryptophan levels. During exercise, the ratio of tryptophan to BCAA increases and, as shown by Blomstrand (38), giving BCAA reduces perceived exertion and mental fatigue and improves cognitive performance *after* exercise.

Agents commonly used in the clinical treatment of fatigue, such as the psychostimulants methylphenidate, dextroamphetamine, pemoline and amantadine act via the dopamine neurotransmitter whereas those currently used to treat depression elevate levels of 5HT. Additional neurotransmitters to consider include histamine, which has an arousing effect on the CNS and histaminergic fibers project diffusely to cortex as discussed above with respect to the ARAS. Clinically, pharmaceuticals with an antihistaminergic mechanism of action induce sedation and fatigue. The novel agent modafinil acts, as one of its known mechanisms, as a histamine agonist. The ARAS is known to utilize cholinergic, histaminergic, glutaminergic and serotonergic neurotransmission (18).

### Endocrine

In populations other than TBI with endocrine abnormalities, especially anterior pituitary dysfunction, a wide variety of symptoms including fatigue are reported. (39–41). Of course, no one hormonal abnormality is correlated exclusively with fatigue and there are numerous other symptoms that are manifested as a result. However in other populations, the association between endocrine dysfunction and fatigue has been particularly well documented in regards to thyroid, growth hormone (GH) and cortisol deficiencies. Deficiencies in GH has been associated with decreased bone mineral densities, (42) aerobic capacity, muscle strength, lower quality of life and cognitive impairments, in addition to increased fatigue (43, 44).

Treating these deficits has been shown to be helpful in other populations. In particular, treatment of GH insufficiency has been shown to increase lean body mass and reduce body fat (45), increase exercise tolerance (46), improve quadriceps strength (47), increase energy and mood (48), increase activity and alertness (49) and an individual's sense of well being and quality of life (50).

The importance of this issue is of course dependent on the overall incidence of endocrine dysfunction associated with TBI. It has been known for nearly one hundred years that brain injury may produce endocrine dysfunction but until recently was considered a relatively rare event (51). Escamilla and Lissner (52) reported an incidence of only 0.7% (4 of 595 TBI subjects) manifesting endocrine dysfunction while Kalisky et al. (53) reported an incidence of only 4% and Edwards and Clark (54) reported a small percentage of TBI cases were associated

with hypopituitarism. However, more recently, the magnitude of the problem has become more evident. Benvenega et al. (55) documented 367 cases of head trauma associated with hypopituitarism. Among these patients, 15% were not diagnosed with pituitary dysfunction till greater than 5 years after injury.

In the past few years, posttraumatic endocrine dysfunction has been studied in a prospective manner. As a result of this work the scientific and medical communities are becoming more aware of the issue of posttraumatic endocrinopathy. Kelley et al. (56) reported that 8 of 22 individuals with TBI had endocrine abnormalities when they underwent provocative testing. Lieberman et al. (51) studied 70 patients with TBI in a postacute brain injury program and identified endocrine abnormalities in 59% of subjects: GHD in 14%, hypothyroidism in 21% and low morning basal cortisol in 45%.

These studies in TBI however only identified the presence of endocrine abnormalities. The relationship between endocrine abnormalities and fatigue in the individual with TBI is an area that is currently under study. In pilot work Doppalapudi et al. (57) have demonstrated an inverse relationship between fatigue and Insulin Growth Factor 1 (IGF1) in persons with TBI. IGF1 is commonly used as a screening measure for GH deficiency because of their correlation. In addition we have noted a direct correlation with a.m. cortisol and subjective reporting of fatigue. While still preliminary, the relationship between endocrinopathy and PTF is exciting as this may potentially lead to an effective treatment.

### Sleep

In general, disturbances of sleep may be characterized as insomnia (deficient sleep initiation or maintenance), hypersomnia (excessive sleep or what is referred to as excessive daytime sleepiness—EDS), and altered sleep-wake cycles (circadian pattern disarray). Sleep disturbances following TBI range in frequency from 36% to 70% (58,59). Several key CNS loci regulate sleep patterns, including brainstem, basal forebrain and hypothalamic nuclei—all areas commonly disrupted in brain trauma. Serotonin and acetylcholine are the two common substances involved. The comprehensive study of posttraumatic sleep disorders is complicated by the frequently encountered comorbidities of depression, anxiety, substance abuse, chronic pain and medication use, all of which independently exert negative influences upon normal sleep. Also not to be overlooked is whether one may implicate a prior (perhaps undiagnosed) sleep disorder as the proximate cause of the brain injury itself. For instance, falling asleep while driving is not uncommon, especially in persons with sleep apnea.

Controversy exists over whether severity of TBI is directly correlated with increased prevalence of insomnia.

Clinchot et al. (60) and Fitchenberg (61) showed an *inverse* relationship and Cohen (62) noted increased prevalence with increasing TBI severity. Some researchers have postulated that the reason for this counterintuitive finding lies in the fact that the severely brain injured likely underreport and the milder brain injured are more aware of their problems and therefore over report or perhaps overly attribute their fatigue to poor sleep. Clinchot et al. (60) examined 100 TBI patients during inpatient rehabilitation and followed them up again one year later. These authors reported that 50% of TBI subjects complained of difficulty sleeping. Of this sub-group 64% admitted waking up too early, 25% experienced increased sleep time, and 45% reported difficulty falling asleep. In this same cohort of 100 patients, 63% reported significant problems with fatigue. Interestingly, 80% of those admitting to sleeping difficulty also admitted to fatigue as a problem. Cohen et al. (62) have pointed to a temporally differentiated sleep disruption pattern whereby difficulty initiating or maintaining sleep tends to occur soon after TBI and excessive daytime sleeping (EDS) tends to occur more often over the months and years following TBI. Controversy also exists over whether TBI may cause a secondary narcolepsy (see Chapter 32 in this book on sleep disorders).

Several varieties of disturbed sleep-wake cycles are seen—the delayed, advanced and disorganized types—with very little literature available specific to the TBI population. Schreiber et al. (63) described sleep-wake disturbance in 15 persons with mild TBI and without history of apnea syndrome, neurological or psychiatric illness. Using polysomnography and actigraphy (activity detection device), more than half were found to have delayed-phase and the rest disorganized type.

Thus, the brain injured population experiences disruption in normal sleep physiology. Specific abnormalities discovered include reductions in REM sleep, sleep spindles, vertex sharp waves and K complexes. These electroencephalographic findings point to an overall decrease in total sleep time, a disappearance of the deeper stages of sleep as well as more frequent awakening (64). Conversely, it has been also found that as cognition improves, so too does REM sleep architecture. There also appears to be an association between cognition and sleep architecture among TBI patients across time so that as the former improves, so too does the latter (65). In addition, it has been well described in the normal, non-TBI injured population, that as sleep time declines and sleep quality worsens there is a decline in cognitive performance as well as an increase in fatigue (66).

Overall, while sleep disturbance after TBI is common, there is little work directly relating this disturbance with fatigue. However, it is likely that the relationship between sleep and fatigue observed in other populations applies to persons with TBI. While these findings are



perhaps predictable, unfortunately even in the normal population we do not know the mechanism whereby sleep reduces the self-perception of fatigue and enhances cognitive performance.

### MANAGEMENT OF PTF

As is the case for most medical conditions in general and neurological conditions in particular, complete cure remains elusive. Nevertheless, it remains critical to start on the road to cure by addressing the fundamentals, relying upon the interdisciplinary treatment team when available. Routine performance of a home exercise program not only optimizes cardiovascular health and physical well being but secondarily enhances important emotional and immune system functioning, which in turn may play important roles in the fatigue experience. Classic rehabilitation practice includes instructing the fatigued individual in compensatory strategies to conserve “energy” and can be tailored to one’s specific functional requirements as they intersect with the particular areas of cognitive functional deficit. The instruction may be as simple as the admonition to *pace* oneself. Psycho-education frequently comprises teaching the person with PTF (and involved caregiver) how the clinical sequelae of focal and diffuse injuries alter the brain’s ability to successfully perform certain tasks that consistently engender fatigue. Therefore, clients may learn how to prioritize activities to meet the goals of daily functioning. When efforts fall short, personal expectations may need to be reconciled with actual abilities and performance (see below). Attempts should be made to counsel those with PTF about dietary habits, with the goal of both weight reduction (given the frequency of post-TBI weight gain) and energy efficiency. At a minimum, obtaining a sleep history should lead to counseling about basic sleep hygiene (see Chapter 32 in this book). When appropriate, more in-depth investigation with polysomnography may reveal a treatable sleep disorder at the root of PTF. As alluded to in the endocrine section, serum hormonal screening may reveal a remediable imbalance although too few studies exist to predict how much success may be expected from a neuropharmacoenocrinologic intervention.

Formal psychiatric care or psychological counseling may be needed to minimize the influence of psychological distress upon cognition and fatigue behavior, through treatment of anxiety and depressive states. Pharmacological management by a professional knowledgeable in TBI leads to the best choice aimed at neutralizing internally distracting states while often parsimoniously addressing other sequelae of TBI such as headache, irritability, perseveration and sleep disturbance. Practically, our bias is to use the most activating of antidepressants

such as fluoxetine, bupropion (whose putative dopaminergic action may also address abulic features), venlafaxine at higher (more noradrenergic) doses, protriptyline and the latest agent, duloxetine, with a novel mechanism of selective noradrenergic and serotonergic reuptake inhibition.

Once modifiable factors have been addressed and conservative measures fail, the first practical pharmacological approach to PTF is to substitute for or eliminate those agents that cause fatigue itself or potentiate any of the common components of PTF. One of the most common obstacles to optimizing efficient cognitive function is the often inappropriately prolonged use of anticonvulsants (67–69) (see Chapter 26 in this book). If post-traumatic epilepsy exists, the least sedating and cognitively debilitating choice of drug must be pursued. Some literature even suggests that one anticonvulsant, lamotrigine, may even be *activating*. Commonly used gastric promotility, anti-spasticity, psychoactive and antihypertensive agents may also hamper optimal cognitive and behavioral (e.g. motivational) function (70).

Regarding clinical use of drugs targeting fatigue, most of the information and experience comes from their use for sequelae other than PTF and from the treatment of fatigue in other disease states. Thus, amantadine has been used sometimes with dramatic effect in TBI to improve various facets of the fatigue experience (e.g. arousal, abulia) and long ago showed efficacy in treating the fatigue associated with MS (71, 72). Numerous papers have reported on the use of methylphenidate, dextroamphetamine, and amantadine to treat cognitive deficits secondary to brain injury and fatigue in other populations. Brietbart and associates (73) demonstrated the benefit of methylphenidate and pemoline in HIV-related fatigue, whereas Wagner and Rabkin (74) reported a similar benefit of dextroamphetamine. Emonson and Vanderbeek (75) reported that dextroamphetamine was also useful for flight crews flying during Desert Shield.

The “classic” stimulants enjoy widespread use in TBI but few, if any, well-designed and powered studies have specifically named PTF as the dependent variable despite the intuitive connection. Until such studies become available, dosing remains mostly symptomatic, aimed at improving function and quality of life. We use short-acting methylphenidate (MP) and dextroamphetamine (DAA), dosed in accordance with their relatively short half-lives, to coincide with therapy sessions or periods of important activity. Long-acting preparations clearly have many advantages but cost remains a major drawback. While these drugs (including *pemoline*) enhance catecholaminergic activity in general, a newer agent, *atomoxetine* is noradrenergic-selective. With this class of stimulant drugs, clinicians should heed the typical cautions (though not seen clinically to a significant degree) (76) to monitor blood pressure and heart rate at a minimum.

The novel wake-promoting agent *modafinil* is known to less-likely cause psychomotor agitation than the classic stimulants, reflecting animal studies showing activation of more subcortical, particularly hypothalamic regions. Originally approved for the treatment of narcolepsy and, more recently, for shift work sleep disorder and under-treated sleep apnea, it does not activate dopaminergic pathways but seems to exert at least part of its action through histaminergic stimulation. Modafinil has been reported to be useful in various populations with neurological disorder including stroke, MS, depression, Parkinson disease and schizophrenia (77). It has also been shown to reduce the fatigue associated with certain medications possessing a sedative side effect.

While its use, too, is often cost-prohibitive, modafinil together with atomoxetine have the distinct advantage of being less *scheduled*, making prescription refills possible and theoretically reducing the risk of medication abuse, which is of particular concern in the largest TBI demographic.

It remains unclear whether treatment with such medications actively ameliorates dysfunction at the level of the supposed fatigue generator, at the behavioral or output level, at the perceptual level; or simply mitigates one to several of the secondary inputs to the ultimate fatigue experience. Given this lack of hard data, the therapeutic relationship may be enhanced through the suggestion that rational trials of complementary or alternative remedies (nostrums?) may, so long as they are not patently harmful, be beneficial. Examples in this category include piracetam (a non-FDA-approved nootropic widely used outside of but obtainable from certain compounding pharmacies in the US), acupuncture and various herbal preparations.

Chapter 57 in this book is dedicated to the pharmacological properties of herbal medication and the readers are referred to that section for an in depth discussion of the material. However, as these agents are becoming more widely used by the medical community (78) and being recommended for the treatment of fatigue (79) a brief discussion is warranted.

Ginkgo Biloba (80) has been suggested as a treatment for many different conditions in numerous populations with suggested doses ranging from 120 to 240 mg a day. Some evidence of its efficacy in the treatment of Chronic Fatigue Syndrome has been demonstrated (81). Ginseng is a complex alternative medication that consists of many compounds and has been suggested to exert its effect through activity on nitric oxide (82). Work by Sorensen and Sonne (83) demonstrated that a dose of 400 mg resulted in improved reaction time. Acetyl-L-carnitine in doses of 1500mg twice a day has been suggested to be beneficial in energy issues and cognitive function post TBI (84). In animal studies it has been shown to be active in the cholinergic system (85) as well as having a neuroprotective effect

on brain cells (86). Citicholine (CDP-choline), which readily crosses the blood brain barrier, dissociates to the acetylcholine precursor choline (84). It has a demonstrated neuroprotective effect and has been widely used in Europe and Asia in the treatment of patients with stroke and TBI. A study by Leon-Carrion demonstrated an improvement in both attention and vigilance (87), with suggested dosing ranging from 1–3 grams per day (84).

## FUTURE DIRECTIONS

The cause of PTF has not been demonstrated to uniquely follow from damage to one particular anatomic locus. The work of Christodoulou et al. (23) and Hillary et al. (24) suggests that neuroimaging may at sometime in the future be better able to correlate deficits in function with morphology. In addition, as neuropharmacological interventions improve and the potential to target medications to specific abnormalities becomes more developed, better treatment outcomes may be obtained. The potential for the use of imaging modalities to select pharmacologic interventions and to predict effectiveness is an exciting prospect. In addition, improved management of endocrine abnormalities, cognitive deficits, mood and sleep disorders may also lead to improved treatment outcomes.

Additional efforts to establish the relationship between fatigue and well known TBI-related deficits, particularly arousal, attention, vigilance, and memory will be critical. The future holds tremendous promise in uncovering the mechanisms of fatigue generation after TBI through a combination of neuroimaging, pharmaceutical interventions and traditional neuropsychological test batteries.

Finally, individuals with TBI have numerous medical issues that differentiate them from other patients who have fatigue. Improvements in the treatment of spasticity, endocrine abnormality, sleep disturbance and mood disorder are just some of the areas where better medical management may make a substantial difference in the nebulous area of the treatment of fatigue associated with TBI.

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# 32

## Sleep Disturbances: Epidemiology, Assessment, and Treatment

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### **SLEEP DISTURBANCES IN TBI: EPIDEMIOLOGY, ASSESSMENT, AND TREATMENT**

**Objectives:** Sleep disturbances in people with traumatic brain injuries, although quite common remains a problematic management issue for caregivers. This chapter will review the epidemiology of sleep disturbances in this population, sleep architecture, sleep neurophysiology, the biochemical pharmacology of sleep, assessment measures and treatment, both nonpharmacologic and pharmacologic. This information will hopefully assist in the decision-making processes of caregivers managing individuals with traumatic brain injury and sleep disturbances.

#### **EPIDEMIOLOGY**

Sleep disturbances occur commonly in patients whom have suffered a traumatic brain injury. The patients may experience sleep disturbances during all stages of recovery. Occurrence rates for sleep disturbances following recent TBI range from 36% (1–3) to 81.2% for hospitalized patients, and 72.7% for discharged patients (4). Disorders of initiating and maintaining sleep (DIMS) were more common among hospitalized patients with recent brain injury. Disorders of excessive somnolence (DOES) were more common in post acute injured patients (4). The total

cost for treatment of insomnia in the U.S. taking into account lost productivity and insomnia-related accidents, may exceed \$100 billion per year (5). Patients whom have suffered a brain injury usually will experience difficulties in many realms of their lives including personal, professional, social, and avocational. Insomnia and sleep disturbances may compound these difficulties due to the fact that disordered sleep can have adverse behavioral and cognitive consequences. Insomnia in the absence of brain injury has been associated with increased absences from work (6), increased health care costs/utilization, and social disability (7). Mahmood et al. (206) hypothesized that TBI patients may experience sleep-related cognitive deficits even without meeting the formal diagnosis of insomnia.

#### **DEFINITIONS OF INSOMNIA**

Primary insomnia is sleeplessness that is not attributable to a medical, psychiatric, or environmental cause.

Secondary insomnia, more commonly diagnosed, is the result of an underlying medical, psychiatric, or environmental condition. Acute insomnia refers to the onset of sleep difficulties caused by emotional or physical discomforts. Acute insomnia could be considered a subset of secondary insomnia.

Sleep-onset insomnia refers to an extended time from going to bed until falling asleep. Circadian

rhythm disorders are considered a subset of sleep-onset insomnias (8).

### CLASSIFICATION OF SLEEP DISORDERS

The International Classification of Sleep Disorders categorizes sleep disturbances as dyssomnias or disorders that result in insomnia or excessive sleepiness; parasomnias or disorders of arousal, partial arousal, or sleep stage transition; and sleep disorders associated with medical or psychiatric disorders (9). An extensive review of the medical conditions that can cause insomnia is beyond the scope of this chapter. However, medical conditions should be considered in patients with sleep difficulties. Table 32-1 includes the most common disorders in each category.

Sleep related breathing disorders are commonly divided into 3 categories: obstructive sleep apnea (OSA), central sleep apnea (CSA), and mixed sleep apnea (11). Obstructive sleep apnea is characterized by periodic apnea

and asphyxia from upper airway obstruction or collapse in the pharynx that continues despite continued respiratory effort. Central sleep apnea is defined as the lack of air-flow accompanied by the lack of respiratory effort. Mixed apneas have components of both obstructive and central apneas (11). Symptoms related to sleep apnea include excessive daytime sleepiness and cognitive difficulties such as impaired memory, loss of judgment, inability to concentrate, irritability, and depression. These symptoms are often present in TBI patients in the absence of sleep apnea making clinical diagnosis difficult (200). Secondary cardiovascular morbidity associated with sleep-related breathing disorders includes systemic and pulmonary hypertension, cardiac arrhythmias, cor pulmonale, stroke, and sudden death (12). Other factors that may be present in the TBI population contributing to fatigue and excessive daytime sleepiness include: electrolyte disturbances, hydrocephalus, occult infection, seizures and endocrine disorders (200).

Webster et al. (200) is one of the first studies of sleep apnea in the traumatic brain injured population.

Restless legs syndrome (RLS) is characterized by unpleasant sensations in the legs or feet that are temporarily relieved by moving the limbs. Symptoms increase in the evening, especially when a person is lying down and remaining still. The dysesthesias cause difficulty falling asleep and are often accompanied by periodic limb movements (13).

Periodic limb movement disorder (PLMD), is characterized by bilateral repeated, rhythmic, small-amplitude jerking, or twitching movements in the lower extremities, and less frequently, in the arms. These movements occur every 20 to 90 seconds and lead to arousals usually not perceived by the patient. The patient complains of not feeling rested. The bed partner often reports these movements. This condition is more common in older individuals (14).

TABLE 32-1

#### Dyssomnias

Intrinsic sleep disorders arising from bodily malfunctions:

- Psychophysiological insomnia
- Obstructive sleep apnea
- Central sleep apnea
- Restless legs syndrome (RLS)
- Periodic limb movement disorder (PLMD)

#### Parasomnias

Group of disorders of arousal, partial arousal, and sleep-stage transition:

- Sleep-walking (somnambulism)
- Sleep talking (somniloquy)
- Sleep terrors
- Nightmares
- Teeth grinding (bruxism)
- REM sleep behavior disorder (RBD)
- Enuresis

#### Medical and psychiatric

- Anxiety
- Chronic pain
- Alcoholism
- Parkinsonism
- Dementia/delirium
- Depression
- Gastroesophageal reflux
- Chronic obstructive pulmonary disease
- Asthma
- Atherosclerotic cardiovascular disease
- Diabetes mellitus
- Thyroid disease (10)

### TREATMENT OF SPECIFIC DYSSOMNIAS OBSTRUCTIVE SLEEP APNEA

The treatment of Obstructive Sleep Apnea partly depends upon the severity of the sleep-disordered breathing. The severity of OSA is defined arbitrarily and differs among centers. The apnea-hypopnea index (AHI) has been used to grade severity of apnea. AHI of 5 to 20/hour is mild apnea; 20 to 60/ hour is moderate apnea; and greater than 60 is severe apnea (137).

Patients with mild apnea have a wider variety of options, while those with moderate to severe apnea should be treated with nasal continuous positive airway pressure (CPAP) (137, 138). CPAP works by splinting the upper airway and preventing soft tissues from collapsing resulting in improvements in apneas and normalizing oxygen saturation (138). The most common side effects of CPAP are dry mouth, rhinitis, and sinus congestion

(138). These can be treated effectively with humidification, antihistamines or nasal steroids. Unfortunately, compliance is a major problem.

Dental devices act by moving the tongue or mandible forward. They can be effective with an AHI of less than 40/hour (139). Dental devices are appropriate first line therapy in mild OSA and can be used as an alternative if the patient does not improve with CPAP (139).

Correction of the upper airway is generally recommended only for patients in whom CPAP has failed, patients who refused to consider CPAP, or those who have very mild OSA (AHI less than 10/hour) (140). The resection of the uvula and soft palate known as uvulopalatopharyngoplasty (UPPP) is effective in about 40% of patients (140). Predicting which patients will benefit from this procedure is impossible. Tracheostomy is another surgical technique that is effective by passing the obstruction. This procedure is indicated for very severe OSA especially when the patient does not tolerate CPAP or has cor pulmonale (140).

### RESTLESS LEG SYNDROME

Patients with Restless Leg Syndrome (RLS) who are sensitive to caffeine, alcohol, or nicotine should avoid these substances (141). Some patients may benefit from different physical modalities, such as hot or cold baths, whirlpool baths, limb massage, vibratory or electrical stimulation of the feet and toes before bedtime (141). Supplementation to correct vitamin deficiencies, electrolytes, or iron may improve symptoms in some patients. Patients with prominent varicose veins in the legs may benefit from TED hose.

Continuous pharmacologic treatment should be considered if patients complain of RLS symptoms at least three nights each week (142). Dopaminergic agents are first line treatment. Levodopa with carbidopa has been shown to improve sensory symptoms and periodic leg movements of sleep (PLMS) in primary RLS and in secondary RLS due to uremia (143). Other dopamine agonists such as Pramipexole, Pergolide, Ropinirole hydrochloride, have been used to treat RLS. Benzodiazepines such as Clonazepam have been shown to ease sensory symptoms and PLMS in RLS (143). Opioids have been used also successfully in decreasing symptoms of RLS (144). Gabapentin is indicated for patients whose symptoms include pain, and/or neuropathy (144).

### NARCOLEPSY

Nonpharmacologic treatment consists of sleep hygiene. Most patients improve if they maintain a regular sleep schedule usually 7.5 to 8 hours of sleep per night (145). Patients with narcolepsy should avoid heavy meals and alcohol (146). A well-designed exercise program can be

beneficial and stimulating (147). Encourage children to participate in after-school activities and sports. School personnel should have the child with narcolepsy refrain from activities if he or she appears drowsy.

Pharmacologic treatment of narcolepsy involves central nervous system stimulants to increase wakefulness, vigilance, and performance, and depressants to reduce cataplectic attacks. Modafinil, an alpha 1-agonist, has been used for several years in Europe to treat narcolepsy and was approved in the United States in 1999 (148). The mechanism of action is not well understood, but it does not appear to alter levels of dopamine or norepinephrine (148). Methylphenidate, the most frequently used stimulant, has been shown to improve sleep tendency in a dose-related fashion (148). Pemoline, the initial drug of choice in children younger than seven with narcolepsy, is a less potent amphetamine that also improves excess daytime sleepiness (EDS) and has relatively little effect on blood pressure (149, 150). Antidepressants such as clomipramine and fluoxetine have been shown to reduce the frequency of cataplexy in narcolepsy.

### TREATMENT OF PARASOMNIAS SLEEP WALKING AND SLEEP TERRORS

Sleepwalking and sleep terrors, especially in children, usually do not necessitate treatment, other than by identifying and minimizing risk factors. Risk factors include: sleep deprivation, pregnancy, menstruation, and specific medications, including psychotropic drugs (eg, lithium carbonate and agents with anticholinergic effects) (151,152). Reports of polysomnographically confirmed cases indicate that most adult cases are not causally related to a psychiatric disorder, although stress can have a contributory role (153). However, in cases involving sleep-related injury (usually in adults), pharmacotherapy is necessary and can be lifesaving. Long-term nightly treatment with a benzodiazepine has been found to be safe and remarkably effective in adults with sleepwalking, sleep terrors, and other parasomnias; the incidences of side effects and misuse or abuse are low (154). Clonazepam (Klonopin), 0.25 to 1.5 mg taken 1 hour before sleep onset, is usually effective. Alprazolam (Xanax), diazepam (Valium), imipramine hydrochloride (Tofranil), and paroxetine hydrochloride (Paxil) also may be used. Use of self-hypnosis techniques can be effective in milder cases in both adults and children. Sleepwalking and sleep terrors are not usually controlled without the treatment of a concurrent psychiatric disorder (152, 153).

### REM SLEEP BEHAVIOR DISORDER

Clonazepam (0.5 to 1.5 mg taken at bedtime) is remarkably effective in controlling both the behavioral and the



dream-disordered components of REM sleep behavior disorder. The long-term efficacy and safety of this regimen have been established (154). In addition, maximizing the safety of the sleeping environment should always be encouraged.

### NOCTURNAL SLEEP-RELATED EATING DISORDERS

Treatment of sleep-related eating is directed at controlling the underlying sleep disorder (155). For cases related to sleepwalking and restless legs syndrome with periodic limb movements, monotherapy or combined therapy with dopaminergic agents (levodopa with carbidopa [Sinemet]), benzodiazepines (clonazepam), and opiates (codeine) can be effective. Fluoxetine hydrochloride (Prozac) and bupropion hydrochloride (Wellbutrin) can also be effective as adjunctive treatments.

### BRUXISM

Psychotherapy has been used to treat bruxism. The belief that bruxism is linked to stress and other emotional and psychological factors gives rise to a variety of psychotherapeutic approaches (156). For instance, calmness and self-confidence, may be fostered by listening to progressive relaxation, visual imagery, or autosuggestion tapes just before going to sleep (157). Another psychological approach to stress reduction resorts to instrumentation. During bruxism, the relevant muscles are active, and this increased activity or tenseness can in turn be measured with an electromyograph (EMG: electro = electric; myo = muscle; graph = record). During treatment sessions at home or the laboratory, the patient sits or reclines comfortably. One or more pairs of recording electrodes are then attached to the surface of the skin, in close contact to appropriate muscles (e.g., masseter muscles). These electrodes transmit information about the level of muscle activity to a computer monitor. The patient is instructed to consciously lower that level below a threshold line (also visible on the screen). Gradually, by becoming alert to the presence of muscle tension, patients may develop techniques for reducing that tension, and hence, bruxism.

One problem with this approach is the expense of the machinery and expert guidance. Another problem is that muscles can be tense for a variety of reasons, and not simply because patients grind or clench. An unpleasant recollection, for instance, may result in a high reading, although it may have nothing to do with bruxism. Moreover, as in the case of many other psychotherapeutic approaches, the training takes place in the daytime, when the patient is awake and when his behavior is under conscious control.

It is not at all clear that such learning is transferable to the unconscious, sleeping brain.

The main problem is the lack of evidence that EMG feedback benefits the patient. In one study, for example, subjects undergoing this treatment for two weeks, along with a program of listening to relaxation tapes, seemed to brux no less than control subjects (who received no treatment) while they were receiving this treatment, or six months after treatment ceased (158).

Another controversial approach is the so-called masked negative practice, a scholarly variation of the folk principle of reverse psychology. Here the patient is told to voluntarily clench the jaw for five seconds, relax it for five seconds, and repeat this procedure five times in succession, six different times a day, for a duration of two weeks (159). Alternatively, the duration of the clenching period may be individually tailored to each patient, with each clench continuing to the point of discomfort (158). This technique involves little or no cost and it does not interfere with the patient's sleep. But, by itself, this approach damages the teeth and may aggravate other bruxism symptoms (160). Notwithstanding early enthusiastic clinical reports, at the moment the evidence for the effectiveness of this approach is meager at best. Pierce and Gales study shows that subjects undergoing this treatment performed no better than controls, while they were receiving the treatment or six months after treatment ceased (158).

Splints are by far the most common treatment regimen for bruxism. Much current research on the treatment of bruxism has been centered on the use of such dental appliances. Many other researchers insist, in fact, that the splint only provides a measure of protection for the teeth, and, in the case of grinders, a moderation of the sound. Some patients find the splint uncomfortable to wear, remove it during sleep, and it may negatively affect one's bite, cause tooth decay, and lead to degenerative joint disease of the temporomandibular joint (161).

In the treatment of bruxism, sleep feedback may involve electromyographic (EMG)-activated alarm (162). Bruxism involves tensing of certain facial muscles. This tensing causes an increase in electrical activity of the muscles, which can in turn be recorded by an electromyograph. The electrodes of this instrument are placed on the facial area where these muscles are located. When the tenseness exceeds a certain predetermined level, the alarm goes off. The loudspeaker can be free standing, or, to prevent waking others, connected to earphones that the patient wears during sleep. This approach is sensible and is fairly unobtrusive, the patient needs not insert anything into the mouth, but needs only attach electrodes externally to the face. On the other hand, this procedure may fail to correct any bruxing behavior, which is associated with muscle tension lower than the predetermined intensity or duration threshold (158, 162). Another obvious problem is that muscle tension may occur in the absence of bruxism.

## SLEEP OVERVIEW

The words sleep and somnolence are derived from the Latin word *somnus*; the German words *sleeps*, *slaf*, or *schlaf*; and the Greek word *hypnos* (15). Hippocrates suggested a humoral mechanism for sleep; sleep was induced by the retreat of blood and warmth into the inner body. Aristotle thought sleep was related to food and heat (15).

Loomis, an American physiologist, and colleagues made the discovery of different stages of sleep reflected in EEG changes in 1937 (16). Aserinsky and Kleitman discovered rapid eye movement (REM) in the 1950's at the University of Chicago (17).

A comprehensive review of sleep architecture is beyond the scope of this chapter. A brief overview is provided.

Sleep is divided into two stages based on behavioral and physiologic characteristics: rapid eye movement (REM) and non-rapid eye movement (NREM).

REM sleep accounts for approximately 20–25% of total sleep time after the age of two years (18). REM sleep is further divided into 2 stages: tonic and phasic. A desynchronized EEG, hypotonia or atonia of major muscle groups, and depression of monosynaptic and polysynaptic reflexes characterizes the tonic phase. The phasic tone is discontinuous and marked by bursts of REM (with rapid eye movements both horizontal and vertical), myoclonic twitches of the limbs and face, and autonomic lability with irregularities of heart rate and respiration with variable blood pressure (19). PGO (ponto-geniculo-occipital) spikes also occur that are not normally seen on polysomnography. PGO activity is a phasic feature of REM sleep, generated in the pons and projected through the lateral geniculate body and other thalamic nuclei to the occipital cortex. It is of 2 types: Type I PGO activity is independent of eye movements, and Type II occurs simultaneously with eye movements (18). Dreams and fragmented images have been associated with PGO spike activity (18).

During REM sleep the brain is very active metabolically, physiologically, and psychologically. This is a result of central activation because the brain neither depends on external stimuli nor expresses a motor output in response to the activation (65). Some authors believe that REM sleep is important to particular brain metabolic processes because of this central activation (65).

NREM sleep accounts for 75–80% of sleep time in adults. It is divided into 4 stages based on EEG criteria. Stage I equals 3–8% of sleep time; Stage II equals approximately 45–55%, Stage III and IV combined equals 15–20% and are described as slow-wave sleep (SWS) (20). Table 32-2 summarizes the distinct differences in the 4 stages.

K complexes are composed of an initial sharp component followed by a slow component. Sleep spindles are episodically occurring rhythmical complexes occurring

**TABLE 32-2**  
*Distinct Differences in NREM Sleep Stages*

STAGE 1
Low voltage
Mixed frequency EEG
STAGE 2
K complexes
Sleep spindles
STAGE 3
Arousal threshold high
Delta waves = 20–50%
STAGE 4
Delta waves = >50%
(19,30)

with frequency of 7–14 cycles per second. They are grouped in sequences lasting 1–2 seconds and can occur alone or can be superimposed on K complexes. They usually arise from gamma-aminobutyric acid (GABA)-ergic neurons in the reticular thalamic nucleus. On scalp recordings, spindles occur maximally over the frontal and vertex areas (18). Sleep spindles may also be found in Stage 3 and 4 NREM sleep or even in REM sleep. They are most characteristic of Stage 2 NREM sleep (19).

Delta waves are high voltage waves (greater than or equal to 75 microvolts), with a frequency range of .5–4 hertz (19,30). Thalamocortical cells are most capable of generating delta or slow waves, but other areas such as the anterior hypothalamus, preoptic region, and basal forebrain are also involved (18).

## ONTOGENY OF SLEEP

Newborns spend about 2/3 of their life sleeping. When they fall asleep they immediately go into REM sleep that is accompanied by restless movements of the arms and legs. At 3 months of age, the REM-NREM cycle is established. Polyphasic sleep progresses to biphasic sleep in preschool kids, and moves to monophasic sleep in adulthood (20). REM sleep patterns remain stable in adults. However, the pattern of REM sleep seen in the young adult with progressively longer periods is not seen in the elderly. Their REM sleep is more equally distributed over the course of the night (21). The proportion of REM sleep tends to decline with deterioration in cognitive function and with specific organic mental disorders (22,23).

## PHYLOGENY OF SLEEP

Many studies have been performed to determine if other mammals have sleep stages. The purpose of these studies is to understand the physiologic and anatomic correlates

of sleep as you ascend the ladder of phylogeny. Tobler (24) concluded that sleep is homeostatically regulated, in a strikingly similar manner, in a broad range of mammals.

Mammals can be long or short sleepers. Small animals that have a high metabolic rate; also have a shorter life span and sleep longer than larger animals with slower metabolic rates (25). Smaller animals also have a shorter REM-NREM cycle. Both vertebrates and invertebrates display sleep and wakefulness (26). Birds show EEG activity of sleep but their REM-NREM cycles are very short (27).

### SLEEP NEUROPHYSIOLOGY

Effector neurons are the neurons directly leading to the production of different REM sleep components. Most of the physiologic events of REM sleep have effector neurons located in the brain stem reticular formation, with important neurons concentrated in the pontine reticular formation (PRF). As REM sleep stages are approaching the PRF neurons undergo depolarization and once reach threshold will generate action potentials. Their discharge rate increases as REM sleep is approached and the high level of discharge is maintained throughout REM sleep (28). Neurons in the midbrain reticular formation, originally described as the ascending reticular activating system, are especially important for EEG activation (28). It is also thought that cholinergic neurons (by excitation of the brain stem reticular neurons), and monoaminergic neurons (using serotonin and norepinephrine) contribute to EEG activation (28). Cholinergic compounds have excitatory actions on approximately 80% of PRF neurons, including those that are important in REM sleep (29).

The laterodorsal tegmental nucleus (LDT) and the pedunculo pontine tegmental nucleus (PPT), are two nuclei at the pons-midbrain junction where cholinergic projections arise in the brain stem. Their rostral projections are important for EEG activation of both REM sleep and waking.

### BIOCHEMICAL PHARMACOLOGY OF WAKEFULNESS

Wakefulness is maintained by the tonic activity of neurons distributed throughout the brainstem reticular formation with projections to the thalamus, hypothalamus and the basal forebrain (31). The dopaminergic and noradrenergic neurons of the ponto mesencephalic tegmentum, the posterior hypothalamic histaminergic neurons, and the cholinergic neurons of the basal forebrain, are the major neurotransmitter systems that appear to regulate wakefulness (31).

Stimulants both increase wakefulness and decrease REM sleep. Withdrawing stimulants in chronic users both

increases total sleep and REM sleep (32). The stimulating effects of amphetamines (33) and cocaine (34) on sleep are suggestive of a role for dopamine in promoting wakefulness. There is no clear-cut role for dopamine in the sleep-wake cycles. Single cell recordings of dopaminergic neurons in the substantia nigra show only minor changes in the sleep-wake cycle (35).

Noradrenergic neurons (found in the locus ceruleus) also have no clear-cut role for sleep-wake cycles. These cells have a state dependent firing rate, a high firing rate during wakefulness that decreases over NREM sleep until they are virtually silent during REM sleep (36).

Histamine has arousing effects and antihistamines have sleep-inducing effects (37–39). An ascending histaminergic pathway from the posterior hypothalamus innervates the cortex, striatum, hippocampus, and amygdala of the forebrain with cell bodies originating in the posterior hypothalamus and midbrain regions (40, 41). Studies suggest that neurons in the ventrolateral pre-optic area (VLPO) of the anterior hypothalamus are involved in the generation of NREM sleep (42). A descending histaminergic pathway extends from the posterior hypothalamus to the mesopontine tegmentum (40,43) where they intermingle with other neuronal projections that play a role in the generation of wakefulness and REM sleep (44, 45). Administrations of substances that impair histamine transmission or synthesis increase NREM, whereas enhancement increases quiet wakefulness (46–48). The role of the H1 and H2 systems is of increasing NREM sleep, and also suggested modulation of the balance between wakefulness and NREM sleep (49).

Cholinergic mechanisms play a clear role in maintaining arousal at both cortical and subcortical sites (50–53). Acetylcholine is released from the hippocampus and the cerebral cortex during REM sleep (54). 5-HT is probably not involved in NREM sleep but rather in the regulation of the stages of sleep. Jouvet et al, postulated that 5-HT, released by axonal nerve endings in the basal hypothalamus as a neurotransmitter during waking, might act as a neurohormone and induce the synthesis or liberation of hypnogenic factors that would be secondarily responsible for NREM and REM sleep (55).

### PHARMACOLOGY OF SLEEP

There are certain substances found within the nervous system that are felt to affect sleep. Since the role of these substances is not well understood, they are discussed separately in the following section.

Delta Sleep-Inducing Peptide (DSIP) is an isolate that is obtained from the blood of rabbits, when in an electrically induced sleep state that induces NREM sleep in recipient rabbits when given by intracerebroventricular infusion (56). These effects are seen with infusions in cats

and rats when given IV or subcutaneously (57). Intravenous infusions of DSIP in humans increased total sleep time regardless of administration times (58–61).

Blood plasma levels of DSIP exhibited a circadian rhythm in both humans and rats with a peak in the late afternoon and a trough in the early morning (62, 63). Not only does DSIP effect sleep but also has many physiologic activities. Graf and colleagues (64) have proposed that in addition to sleep facilitation, DSIP may also exert a chronopharmacologic action as a natural programming substance by inducing changes in cerebral neurotransmitters and plasma proteins.

Sleep-promoting substances uridine and SPS-B are both implicated in the more frequent occurrence of NREM and REM sleep episodes with normal sleep-waking behavior (65).

Muramyl peptides are proposed to induce sleep, which in turn enhances immunoreaction, serving a recuperative function in the mammalian body. A muramyl tripeptide isolated from humans is an active somnogen (66–69). Muramyl peptides are peptidoglycans that form the backbone of bacterial cell walls and exert profound pyrogenic and immunostimulatory activities in the mammalian body (70–72).

Krueger et al. (67) proposed that sleep has a reciprocal relationship with the immune system. Sleep is enhanced by certain immune modulators, and may enhance certain aspects of immune regulation. Interleukin-1 belongs to a family of polypeptides that mediate a variety of host-defense functions and possess pyrogenic activity. It is liberated by macrophages to activate T lymphocytes and induce fever by acting on hypothalamic cells. IL-1 and other immune modulators have been found to be elevated in humans during sleep (73). This peak in plasma levels occurs during SWS shortly after sleep onset (73).

A naturally occurring peptide isolated from the pineal gland, arginine vasotocin, modifies conditioned behavior, inhibits gonadotropin release, and possibly enhances NREM sleep (65).

Caffeine shortens REM latency and decreases sleep, particularly NREM sleep, presumably through its blockade of adenosine receptors. Adenosine is a naturally occurring purine nucleoside that causes sedation and inhibits neuronal firing activity (74). Extracellular concentrations of adenosine decrease with sleep. It is suggested that the duration and depth of sleep are increased by elevated concentrations of adenosine after waking (65).

The prostaglandin-dependent humoral theory of sleep regulation was developed by Ueno et al. (75,76) and Matsumura et al. (77). Two different prostaglandins: PGD<sub>2</sub> and PGE<sub>2</sub> have been shown to work reciprocally to affect sleep. When PGD<sub>2</sub> increases, PGE<sub>2</sub> decreases sleep time in a dose-dependent manner (75–77). Reciprocal activities of the PGD<sub>2</sub> and PGE<sub>2</sub> in or near the preoptic area and posterior hypothalamus may regulate the

state of vigilance (78).

Melatonin is a major hormone secretion of the pineal gland in mammals. The synthesis and release is timed by one or more biological clocks but occurs only in humans after dark. Melatonin is purported to have sleep-inducing properties (79) in cats, rats, young chickens, and humans (81–85). Its physiological actions include a phase-shifting effect on circadian rhythms, increased sleepiness when administered during daytime hours, and vasoconstriction (13). It can also be used for the treatment of jet lag and delayed sleep-phase syndrome (80). Melatonin secretion at night generally decreases as normal and pathologic aging occurs. Whether this natural process is associated with poor sleep is unknown, despite claims by numerous authors that exogenous melatonin restores natural sleep (65). It is unlikely that melatonin has any direct effects on sleep regulation secondary to the high doses needed, however it may affect sleep indirectly by altering the phase of the circadian pacemaker (86).

GABA has a role in sleep induction through the use of benzodiazepine medications, which enhance GABAergic inhibitory transmission (87). They also aid sleep through anxiolytic and muscle relaxation mechanisms.

## ASSESSMENT OF SLEEP DISTURBANCES

Patients need to be asked specific questions about their sleeping habits and difficulties at each visit. It is very helpful for both physician and patient, to have the patient keep a sleep diary for a specific period of time. A period of 2 weeks to 1 month has been suggested by various authors. The patient is to record a night-to-night history of their sleeping schedule and perception of sleep quality. This information may enable the clinician to identify modifiable causes for the sleep difficulties.

Table 32-3 provides a concise representation of the approach to sleep disturbances.

## INSOMNIA QUESTIONNAIRES

Various questionnaires have been developed to aid in the diagnosis of insomnia within the general population. Recently published examples include the Epworth

**TABLE 32-3**  
*Approach to Sleep Disturbance*

- Comprehensive evaluation of insomnia
- Sleep hygiene measures
- Environmental alterations
- Behavioral/cognitive therapies
- Pharmacological treatment

Sleepiness Scale (88), The Sleep Disorders Questionnaire (89), and the Pittsburgh Sleep Quality Index (90). The difficulty lies in correlating these questionnaires to patients who have suffered a traumatic brain injury. Few formal measures were found to be validated in a population characterized with TBI. Other helpful questionnaires when evaluating patients with TBI who report sleep difficulties include:

The Beck Depression Inventory (91) and the Multidimensional Pain Inventory (MPI) (92). The Beck Depression Inventory consists of 21 items, each of which requires the respondent to rate the presence or absence of a specific sign of mood disturbance on a 4-point scale. It provides information on the cognitive, affective, and somatic aspects of depression (91).

The MPI consists of 61 items that requires patients to rate the magnitude of various pain-related problems on a 7-point scale. It evaluates an individual's experience of pain from a psychosocial perspective and contains measures of self-perceived pain intensity and pain interference with functional activities (92).

The Sleep Disorders Questionnaire has 43 questions related to various medical conditions and symptoms as reported by the patient and the family members that are applicable in the past six months. It is very helpful to not only assess actual symptoms related to insomnia, but also the patient's perception of those symptoms.

The Epworth Sleepiness Scale evaluates daytime alertness by asking the patient to rate the likelihood of dozing or falling asleep in eight different situations, such as conversing with another person, riding in a car, resting after lunch, and reading a book. It uses a 4-point scale and has been shown to possess good sensitivity and specificity to sleep apnea, narcolepsy, and hypersomnia (88).

The Multiple Sleep Latency Test (MLST) can be ordered to determine the severity of sleepiness and give an indication of the presence or absence of the early onset of REM sleep (93). It is the only scientifically validated objective test of excessive sleepiness and is used to establish a diagnosis of specific sleep disorders or to determine the severity of sleepiness. This test is indicated for all patients suspected of narcolepsy to confirm diagnosis and severity of sleepiness; patients with mild to moderate obstructive sleep apnea syndrome who complain of moderate to severe sleepiness; in evaluation of patients suspected of having idiopathic hypersomnia, periodic limb movement disorder or when the cause of excessive sleepiness is unknown (166, 168). The MSLT is indicated in the evaluation of the complaint of insomnia when the presence of moderate to severe excessive sleepiness is suspected, and is useful in assessing the response to treatment following effective therapy for disorders that cause sleepiness to ensure occupational safety (167).

The MLST consists of five 20-minute nap opportunities, with each nap separated by 2 hours. The patient

lies in a dark room and attempts to sleep. The time before sleep is recorded for each nap, and the mean latency for all 5 naps is determined. Patients with a mean sleep latency of < 5 minutes are considered to have pathological sleepiness and those who fall asleep between 5–10 minutes are considered normal. Sleep is staged during the naps. If REM sleep occurs during 2 or more naps, the test is consistent with a diagnosis of narcolepsy, if other causes of sleep-onset rapid movements have been excluded (94).

The Pittsburgh Sleep Quality Index (PSQI) examines sleep quality and disturbances for a 1-month period. Patients provide specific sleep-related information including: usual bed time, rising time, minutes to fall asleep, and hours of actual sleep each night. They also rate a variety of sleep-related factors on a 4-point scale including: subjective sleep quality, use of sleep medications, daytime alertness and mood, and sleep disturbances such as nighttime awakenings, respiratory distress, physical discomfort, and disturbing dreams (90). Poor sleepers and insomniacs are readily identified by the PSQI and it is well suited for research examining general sleep patterns and problems (90). The PSQI was demonstrated to be a valid and useful screening tool for assessing insomnia and sleep difficulties among patients with postacute TBI (95). Steele et al. (192) have studied the effect of TBI on the timing of sleep but have concluded that the Morningness-Eveningness Questionnaire (MEQ) may not be suitable for use in a cognitively impaired patient population.

### OBJECTIVE SLEEP TESTING MEASURES ACTIGRAPHY

Actigraphy is a method utilizing a portable device, to study sleep-wake patterns and circadian rhythms by assessing movement, most commonly at the wrist. Actigraphy is reliable and valid for detecting sleep in normal healthy populations, but less reliable in disturbed sleep (163). Actigraphy is not indicated for the routine diagnosis, assessment of severity, or management of any of the sleep disorders, including the insomnias, obstructive sleep apnea syndrome and periodic limb movement disorder (163). Actigraphy may be a useful adjunct to modified portable sleep apnea testing when determining the rest activity pattern during the testing period (164). Actigraphy is an effective means of demonstrating multi day human rest-activity patterns and may be used to estimate sleep-wake patterns in the occasional clinical situations where a sleep log or diary cannot provide similar information (165). Actigraphy may also be useful in characterizing and monitoring circadian rhythm patterns or disturbances in the elderly and nursing home patients with or without dementia; newborns, infants, children, and adolescents; hypertensive individuals; depressed or schizophrenic patients; and individuals in inaccessible situations (space flight) (163).

## POLYSOMNOGRAPHY

Polysomnography (PSN), is routinely indicated for the diagnosis of sleep-related breathing disorders; for continuous positive airway pressure titration in patients with sleep-related breathing disorders; for documenting the presence of obstructive sleep apnea in patients prior to laser-assisted uvulopalatopharyngoplasty; with a multiple sleep latency test in evaluation of suspected narcolepsy; or when there is a strong clinical suspicion of periodic limb movement disorder (169, 170). Diagnosis of narcolepsy and posttraumatic hypersomnia requires a MSLT after a relatively normal night's sleep as documented by nocturnal PSN (201). Guilleminault et al. (193) found a MSLT score  $<10$  in 82.6% and sleep disordered breathing in 32% of patients with head or neck trauma. PSN is not indicated for the diagnosis of circadian rhythm sleep disorders or to establish a diagnosis of depression (170). Masel et al. (202) concluded that due to patients inability to perceive their hypersomnolence, a sleep laboratory evaluation should be considered part of their medical management.

## NONPHARMACOLOGIC MEASURES FOR TREATING SLEEP DISTURBANCE

Nonpharmacologic measures should be attempted in all patient populations, not only those with TBI and should be undertaken as quickly as possible once insomnia and sleeping difficulties have been identified. Sleep hygiene refers to health practices and environmental influences on sleep. The following suggestions should be of benefit to all patient populations affected:

- Awake at the same time daily.
- Limit total daily caffeine consumption and discontinue consumption 4 to 6 hours before retiring.
- Nicotine is a stimulant and should be avoided in all forms.
- Do not eat heavily close to bedtime.
- Sleep may be enhanced by performing a regular exercise program in the late afternoon or early evening at least 3 hours before bedtime.
- Move the clock out of view from the bed.
- Maintain the sleeping environment as comfortable as possible, minimize noise, light, and excessive temperatures (13).

## STIMULUS CONTROL INSTRUCTIONS

A set of techniques to establish sleep/wake patterns, cues for sleeping, and reduction of associations with activities that interfere with sleep:

- Lie down when feeling sleepy.

- If having difficulty with sleep, leave the bedroom. Return to bed when sleepy. The goal is to develop a positive association between the bedroom and sleep.
- Use the bedroom only for sleep and sexual activity.
- Awake at the same time each day.
- No napping (10).

## SLEEP RESTRICTION

The goal of this treatment measure is to increase the percentage of time in bed asleep. The patient limits the amount of time spent in bed to the actual time that is spent sleeping. The type of treatment often results in a mild sleep deprivation state initially that should promote more rapid sleep onset and more efficient, restorative sleep. The rising time should remain constant and the bedtime altered to maintain a regular sleep/wake rhythm. For example, if a patient only reports sleeping 4 hours a night but arises at 5 AM daily, then he should stay up until 1 AM. Each night they will go to bed 15 minutes earlier. This procedure is followed over several weeks until the desired sleep duration is achieved. This type of treatment is modified for older patients by allowing them to take an afternoon nap (13).

## ENVIRONMENTAL MEASURES CHRONOTHERAPY

Chronotherapy is a treatment measure developed primarily for circadian rhythm disorders in which the individual's sleep/wake cycle is out of phase with the bedtime (96). This treatment is very effective for patients with delayed sleep phase syndrome, who exhibit difficulty falling asleep at night and report feeling tired in the morning when awakened. The patient's bedtime is delayed by daily increments of 3 hours until sleep onset coincides with the desired bedtime (97).

## BRIGHT LIGHT THERAPY

This treatment has also been used for a number of circadian rhythm disorders. Research has shown that properly timed exposure to bright light (7000–12,000 lux) for 2–3 days can shift the phase of the sleep rhythm (98). As a frame of reference, typical indoor room light is  $<500$  lux; a few minutes after dawn, sunlight produces about 2500 lux; and at noon, sunlight is ~100,000 range (99). It is also important to have periods of darkness without bright light (98).

## CRANIAL ELECTROTHERAPY STIMULATION

CES (Cranial Electrotherapy Stimulation) is a process, which utilizes minute electrical stimulation for therapeutic treatment of anxiety, depression, and insomnia (184).

Applied through electrodes to the area between the mastoids and the jaw, the sensation felt by the individual is normally one of relaxation (184). If there is high stress or anxiety just prior to treatment, the individual may go to sleep while using CES, particularly if sitting in a reclining position (184). Sleep at the time of application is not required to benefit from CES, although individuals frequently report an improvement in the quality of their night time sleep (184). As with a number of medications, the mechanism of action of CES is not fully understood. Research has led to the hypothesis that CES has a mild effect on the hypothalamic area of the brain (185, 186). Researchers also have noticed rapid increases in serotonin, also associated with relaxation and calmness, and decreases in cortisol, one of the primary stress-related biochemicals (186,187). Interestingly, CES also increases levels of norepinephrine and dopamine, both associated with alertness and feelings of pleasure (187). No negative effects or major contraindications have been found from the use of CES to date, either in the US or other parts of the world.

### **BEHAVIORAL AND COGNITIVE THERAPIES**

Cognitive therapy involves identifying dysfunctional beliefs and attitudes about sleep and replacing them with more adaptive substitutes (13). The primary goal is to change the patients' view of the sleep problem from one of a victim, to one in which they are capable of developing adaptive coping skills. These changes in their way of thinking often helps to decrease the anxiety the patient experiences, thereby facilitating sleep. Paradoxical intention is the approach that instructs the patient who has difficulty falling asleep to stay awake as long as possible. Multiple studies have evaluated this technique with mixed results regarding its effectiveness (97).

### **RELAXATION THERAPY, MEDITATION, AND BIOFEEDBACK**

Many patients are anxious and have high levels of arousal that interfere with their ability to fall asleep. The goal of this treatment is to allow the patient to relax and fall asleep more easily. These therapies are useful for both sleep-onset and sleep-maintenance insomnia problems (97).

### **SLEEP DIFFICULTIES SPECIFICALLY RELATED TO TBI**

The emergence of insomnia after TBI concerns treatment providers, because as Zafonte et al (101) have noted, disordered sleep can have adverse behavioral and cognitive

consequences. Patients with TBI are prone to depression, particularly the mild TBI patient. Strong correlation exists between insomnia and depression in the non-TBI population. Insomnia is a common feature of depression. Both Beetar et al (103) and Fichtenberg et al. (102) find an association between insomnia and mild brain injury. It is not surprising that there is an association between insomnia and depression in the post-acute TBI patient. This follows the course of recovery after TBI. During the acute stage, dysregulation of sleep seems to be a function of the diffuse disruption of cerebral functioning in the wake of both direct physical damage to the brain and secondary neuropathological events. Sleep abnormalities are more likely to occur in patients with lesions in the pontine tegmentum located in the midpontine region (100). As brain functioning becomes reorganized and some degree of neurological stability is reestablished, sleep can be expected to normalize in the absence of damage to neural sleep structures (104). Insomnia is linked to both depression and mild brain injuries. The determinants of insomnia and depression may differ from the acute and the post-acute stage. Neurological factors may play a role in the early recovery process, and psychosocial factors may contribute later (104). When assessing insomnia in the brain-injured population, it is imperative to diagnose depression, as well as other psychiatric and emotional disturbances.

Changes in sleep patterns in patients that have suffered a traumatic brain injury are fairly common. Reports have shown decreased REM and slow wave sleep, as well as an increase in the number of times an individual awakens during sleep (105). Brain injury is believed to contribute to a shortening of the total sleep time and the disappearance of deep sleep (106). Sleep complaints of patients with brain injury are found to correlate with the presence of fatigue, higher Glasgow Coma Scale scores, better immediate memory, a positive substance abuse history, older age, and female gender (107). Sleep complaints are common in patients with recent injury, and those sustaining injury 2–3 years previously (105). Disorders in initiating or maintaining sleep (DIMS) occur more often in patients with recent injury, and disorders of excessive somnolence (DOES) occur more often in those patients with injuries sustained 2–3 years prior (105). TBI may also result in sleep apnea, which can have obvious effects on sleep maintenance (103).

### **ALTERNATIVE/COMPLEMENTARY MEDICINE TECHNIQUES**

Various methods of alternative/complementary medicine may be helpful in facilitation of sleep including: acupuncture, aerobic exercise, massage, ultrasound, cranial electrical stimulation, and reflexology. Every patient must be

questioned about the presence of pain and its interference with sleep. Aggressive evaluation, intervention and treatment of pain in both TBI and non-TBI patients is warranted. Treatment of the patient's pain may facilitate sleep.

## MELATONIN

Melatonin is a hormone synthesized in the pineal gland and, to a lesser extent, in the retina. Melatonin's excretion, which peaks after dark, follows a day/night rhythm not only in humans but also in all species studied, and is responsible for sleep induction. Physiological concentrations of melatonin can stimulate the release of opioid peptides by activated T-helper lymphocytes (180). These melatonin-induced-immuno-opioids (MIIO) mediate the immunoenhancing and anti-stress effects of melatonin and cross-react immunologically with anti-beta-endorphin and anti-met-enkephalin antisera (180). Studies have also shown the hypnotic effect ascribed to melatonin is exerted through its effect on the thermoregulatory mechanism (181). Those authors believe that by lowering core body temperature, melatonin reduces arousal and increases sleep propensity (181). Melatonin has also been shown to accelerate sleep initiation, improve sleep maintenance, decrease sleep stage 1 and increase sleep stage 2 (182). The influence of exogenous melatonin on the sleep-wake cycle was investigated. Sleep onset time and wake time were significantly earlier when using melatonin than during placebo (183). Contraindications for the use of melatonin include: heart disease, atherosclerosis and stroke secondary to vascular constriction effects. It may also negatively affect fertility (195). Fluoxetine decreases melatonin levels; TCA's and fluoxetine increase melatonin concentrations (195).

Research shows that a number of natural sleep aids may benefit anyone involved in the pursuit of a good night's rest. Valerian, kava kava, hops, passionflower have all been shown to improve sleep quality. The German government and European community sanction these herbs for the treatment of insomnia.

The active chemical constituents of valerian are primarily the valepotriates, which possess sedative activity (171). The valepotriates weakly bind GABA-A receptors. Sedation in the central nervous system is primarily controlled through these receptors. Because valerian weakly binds these receptors, its sedative actions do not result in dependence and potential addiction (171). Numerous human sleep studies have demonstrated that valerian produces a significant improvement in sleep quality, and an increase in deep REM sleep (dream phase) without producing the side effects of sleep drugs (172).

Kava kava is recognized for the ability to produce relaxation without the loss of mental sharpness (173). The active constituents of Kava consist of a group of lactones similar in structure to gamma-butyrolactone, (GBL)

a precursor to gamma hydroxybutyrate (GHB) (173). GHB produces sleepiness and depresses the dopaminergic pathway when given in high doses (173). Numerous clinical and experimental studies have documented the relaxing, sleep-promoting and anti-anxiety actions of kava extracts that contain high levels of Kava lactones. In a 1991 double-blind, placebo-controlled four-week study of patients suffering from anxiety, a group receiving kava lactone extract three times daily showed reduction in anxiety after just one week and were significantly improved at the end of the study (173). The kava group experienced a significant reduction in menopausal symptoms, anxiety and depression compared to the control group (173). A study compared the effects of a kava lactone to oxazepam (a benzodiazepine drug) in patients suffering from anxiety for four weeks. Each substance reduced symptoms of anxiety equally (174). The kava lactone produced no negative side effects and oxazepam produced side effects such as drowsiness, dizziness, headaches and vertigo (174).

Passionflower was listed in the National Formulary from 1916 to 1936 and approved as a sedative and OTC sleep drug (175). Italian researchers tested Passionflower alone and in combinations with other sedative herbs (175). They observed a synergistic effect of sedative activity from the herbal combinations. Studies have shown that oral administration and injections of passionflower into rats prolonged sleeping time, protected animals from convulsive chemicals and relaxed their muscles (175).

Hops are extensively used in botanical formulas for the treatment of insomnia because they influence relaxation in the central nervous system (176). They are recommended by herbalists to ease tension and anxiety, and may be used when tension leads to restlessness. Studies have demonstrated equivalent efficacy and tolerability of a hop-valerian preparation compared with a benzodiazepine preparation in patients suffering from sleep disorders (176). The researchers concluded that a hop-valerian preparation in the appropriate dose is a sensible alternative to benzodiazepines for the treatment of non-chronic and non-psychiatric sleep disorders (177).

Chamomile is derived from the flower heads of either of two annual plants: German chamomile (*Matricaria recutita*), or Roman chamomile (*Chamaemelum nobile*) (178). Chamomile is a popular folk remedy for digestive problems, fever, menstrual discomfort, stomachache, and anxiety. It is used to treat insomnia in children because it is a very mild relaxant and has a pleasant taste (178). Flavonoids such as apigenin as well as a distinctive blue essential oil (azulene) derived from chamomile have been found to reduce inflammation and encourage the healing of wounds (179). Apigenin may also be responsible for chamomile's anti-anxiety and sedative effects, via action on central benzodiazepine drug receptors (179). Both oral and topical chamomile



products are considered nontoxic and gentle enough for use in children or pregnant and lactating women (178).

### PHARMACOLOGIC TREATMENT FOR SLEEP DISTURBANCES

All psychosocial and physical aspects must be taken into consideration when prescribing medications to patients with traumatic brain injury. Every patient's unique and individual circumstances will affect medication choices.

#### ANTIHISTAMINES

Antihistamines are frequently purchased over-the-counter to produce or enhance sleep. When utilized by patients that have sustained a traumatic brain injury, they may produce negative cognitive effects by means of their anticholinergic actions (101). Furthermore, in studies by Roth et al. (114) and Nicholson (115, 116), it was shown that traditional antihistamines produced increased daytime sleepiness, most clearly apparent at the usual nadir in the circadian cycle of alertness. In these studies, however, antihistamines such as loratadine (in doses of 10 and 40 mg), terfenadine, and astemizole were not associated with these undesired side effects.

#### ANTIEPILEPTICS

Drowsiness and lethargy are often reported side effects of anticonvulsant medications. Caregivers using these medication(s) in patients with traumatic brain injury must keep in mind the potential undesired side effects on sleep and arousal that may be produced (101). Phenytoin administration long-term produces a decrease in sleep onset latency, a transient increase in SWS, and possibly a transient reduction in REM sleep (109, 117, 118). Carbamazepine produces a decrease in stage I sleep, an increase in SWS, and an increase in total sleep continuity (101, 109). Sodium valproate tends to increase total sleep time by decreasing total awakenings (119).

Gabitril (tiagabine) a newer, well-tolerated anticonvulsant, is rapidly absorbed after oral administration, has an elimination half-life of seven to nine hours (120).

Tiagabine significantly increased sleep efficiency by increasing SWS, caused by changes in stages 3 and 4, especially during the second and third two-hour intervals of the sleep period (121). The promotion of deep sleep was further corroborated by elevations in slow-wave activity within non-REM sleep. Tiagabine had demonstrated no effect upon sleep onset latency or total time spent in bed (121).

Pregabalin is a gamma-aminobutyric acid (GABA) analogue that binds to calcium channels, not GABA

receptors, and modulates calcium influx, resulting in antiepileptic, analgesic, and anxiolytic activity. (122, 123). It has shown greater potency than gabapentin in pain and seizure disorders (124).

Pregabalin has shown increased duration of nonrapid eye movement sleep, decreased rapid eye movement sleep, and did not affect sleep onset latency (125).

#### ANTIDEPRESSANTS

Antidepressant medications may impact sleep patterns both directly (by means of suppression of REM sleep and prolongation of REM latency) (126) and indirectly (e.g., by their effect on the underlying depression and its associated sleep disturbances (109)). Monoamine oxidase inhibitors cause the greatest suppression of REM sleep, perhaps therapeutic in that regard, because the depressed patient may be experiencing excessive REM sleep (127). The tricyclic antidepressant drugs and selective serotonin reuptake inhibitors also lead to varying degrees of REM sleep suppression. According to Arew (128), the primary indication for tricyclic antidepressants in treating insomnia is the patient whose sleep problems are secondary to depression. Nefazodone and Remeron, newer generation antidepressants unrelated to the SSRIs, tricyclics, and monoamine oxidase inhibitors, improve sleep initiation secondary to sedating side effects. Exact mechanism is unknown; however, it is presumed to be by means of serotonergic mechanisms (101). A newer agent, mirtazapine has serotonin blocking properties and has been shown to improve sleep architecture and efficiency (208).

#### SEDATIVE/HYPNOTICS

Historically, the benzodiazepine class of medications has been most commonly prescribed for insomnia and has demonstrated efficacy in short-term treatment (108).

The hypnotic agents act by means of gamma-aminobutyric acid (GABA) transmission through modulation of chloride channels to decrease phasic interruptions of sleep and increase total sleep time (101). Activation of the benzodiazepine receptor leads to an increase in GABA. This class of medications can produce a variety of side effects including physical dependence, sedation, and impairment of motor and cognitive abilities. This class is typically used for 4 weeks. Long-term use can have the potential for habituation and withdrawal symptoms. More effective long-term management of insomnia is attained if these medications are used in conjunction with behavioral therapy techniques (112). Agents with a shorter half-life should be prescribed first, since they are eliminated from the system by morning, decreasing the likelihood of

residual daytime effects. These agents may improve sleep during the first part of the night, but can lead to withdrawal-like syndromes, with REM sleep rebound and sleep fragmentation during the latter part of the night (109). Sedative and hypnotic medications can also worsen sleep apnea syndromes (109).

Zolpidem (Ambien), although not a true benzodiazepine, is often included with the class because the site of action is the benzodiazepine receptor site (110). Most hypnotic agents bind to three omega receptors; zolpidem has an affinity for the omega 1-receptor (101). It also seems to preserve stage 3 and 4 sleep and produces only minor inconsistent changes in REM sleep (111). Ambien, enhances the brain's major inhibitory neurotransmitter, gamma aminobutyric acid (GABA). GABA receptors are located in the cerebellum and cerebral cortex, but not in the spinal cord or peripheral tissues (188). Ambien in vitro preferentially binds to a subunit of the GABA receptor (also called the benzodiazepine receptor) (188, 190). Although Ambien binds to the benzodiazepine receptor, it is an imidazopyridine with chemical structure unrelated to benzodiazepines or barbiturates (189, 190). While these drugs share some of the pharmacologic properties of benzodiazepines, they differ in binding to receptor cells in the GABA complex, producing sedative, muscle relaxant, anti-convulsant and anxiolytic effects. Imidazopyridines selectively bind to just the receptor cells responsible for sedation, thereby producing less side effects and less potential for addiction (188,189).

The longer acting agents flurazepam (Dalmane) and quazepam (Doral) can cause daytime sleepiness but are less likely to produce rebound insomnia (108). Benzodiazepines are preferred to barbiturates and other agents such as chloral hydrate. Chloral hydrate is often used in TBI patients, because it affords rapid sleep induction without increasing the seizure threshold (109). It is not recommended for treatment of insomnia in the general population because of the narrow therapeutic ratio, rapid development of tolerance, systemic toxicity, potential for abuse, and the possibility of severe clinical complications of withdrawal (13). Sonata is a hypnotic agent with a chemical structure unrelated to the benzodiazepines, barbiturates, and other drugs with hypnotic properties. It has been shown to decrease the time to sleep onset. It has not been shown to increase total sleep time or decrease the number of awakenings (113). Eszopiclone, a new non-narcotic, non-benzodiazepine hypnotic, is indicated for improved sleep maintenance. It is the first and only hypnotic agent at publication approved for long-term use with no tolerance observed in a 6-month trial (209).

### ANTIPSYCHOTICS

This class of medications, have both direct effects on sleep and the ability to promote sleep by attenuating symptoms

that interfere with sleep, such as psychosis and agitation. As a group, they increase daytime somnolence, total sleep time, REM percentage of total sleep, and sleep continuity. The antipsychotic drugs also lead to decreased sleep latency and percentages of sleep in stages 1 and 2 (129–133).

### LITHIUM

Chesnik and Mendels have pointed out that lithium has multiple effects on sleep/wake patterns (134). It increases the percentage of stage 2 and SWS, the REM latency, and the total sleep time. The obvious assumption follows that it also increases daytime somnolence, a hypothesis that has proven true in most clinical cases (135).

### OPIATES

Opiates promote feelings of peacefulness, drowsiness, and pain-relief that lead to the impression they are promoting sleep. There is noted psychomotor slowing. The strong analgesic properties may permit sleep in people who would otherwise be unable to do so, such as those with chronic pain syndromes or restless legs syndrome (109). Although not borne out by polysomnographic changes in sleep, narcoleptic patients treated with codeine report better sleep (136). Patients who have suffered acute traumatic brain injury often have associated fractures and injuries. They may derive sleep benefits from treatment of their pain using opiates.

Table 32-4 organizes the medications by class and their documented effects on sleep.

### CONCLUSION

Insomnia and sleep disturbances are common complaints of both the general patient population as well as the brain injured populations. The architecture of sleep, assessment of sleep disturbances and insomnia, and treatment methods; both nonpharmacologic and pharmacologic have been reviewed. Prescription medications affecting the sleep cycles were reviewed in detail, and common effects compared and contrasted.

Once a sleep disturbance has been identified and investigated, a plan of care is formulated. The least-invasive techniques should be utilized initially and followed by prescription sleep aids if the symptoms fail to resolve. All psychosocial and physical aspects must be taken into consideration when prescribing medications for patients with TBI. It has been suggested that serotonergic agonists (trazodone, doxepin, amitriptyline) be used for sleep initiation problems. Sleep maintenance problems may be more efficiently handled with catecholaminergic agonists (nortriptyline) (137).

**TABLE 32-4**  
**Medications by Class and Their Effects on Sleep**

MEDICATION TYPE	DRUG	INCREASES OR POSITIVE EFFECTS ON SLEEP
Antihistamine	H1 antagonists: Diphenhydramine Loratadine Terfenadine	Daytime somnolence
Antiepileptics	Clonazepam Valproate sodium Carbamazepine  Phenytoin Tiagabine  Pregabalin	Stage 4% Daytime somnolence Daytime somnolence Sleep continuity in epileptics SWS% (transient) Sleep efficiency SWS Enhancement of slow EEG components Nonrapid eye movement sleep Pain-relief Somnolence Anxiolytic
Antidepressant	Selective serotonin reuptake inhibitors: Fluvoxamine Fluoxetine Tricyclic antidepressants: Doxepin Clomipramine Desipramine Nortriptyline Amitriptyline Imipramine Serotonergic agent: Trazodone  Nefazodone  Remeron	Sleep latency REM latency  Total sleep time Stage 2% Daytime somnolence REM latency  Daytime somnolence Sleep continuity SWS% REM latency Sleep initiation Sleep continuity Sleep initiation
Sedative/Hypnotic	Benzodiazepines: Triazolam Temazepam Quazepam Nitrazepam Midazolam Lormetazepam Flurazepam Zolpidem  Barbiturates: Amobarbital Secobarbital Phenobarbital Pentobarbital Chloral hydrate  Sonata	Total sleep time Sleep continuity Stage 2% REM latency  Sleep continuity SWS% Daytime somnolence Total sleep time Sleep continuity Stage 2% REM latency Total sleep time Sleep induction Sleep initiation

TABLE 32-4 (continued)

MEDICATION TYPE	DRUG	INCREASES OR POSITIVE EFFECTS ON SLEEP
Antipsychotic	Haloperidol, trifluoperazine, loxapine, chlorpromazine	Sleep continuity Daytime somnolence Total sleep time REM%
Lithium		Daytime somnolence Total sleep time SWS% Stage 2% REM latency
Opiate	Morphine, codeine, heroin	Pain-relief Daytime somnolence

Comprehensive evaluation and interpretation of the patient's symptoms combined with the information in this chapter should allow formulation of a safe and effective treatment plan for sleep difficulties in patients with traumatic brain injury.

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# 33

## Diagnosis and Management of Late Intracranial Complications of TBI

*David F. Long*

### INTRODUCTION

#### Purpose and Overview

*Purpose* Although many patients show excellent progress during rehabilitation from traumatic brain injury (TBI), intracranial complications occur frequently and can result in an adverse outcome. In many instances, prompt and accurate diagnosis of these complications can either be life-saving or can dramatically improve the extent of recovery which takes place.

*Overview* Complications addressed in this chapter include central nervous system (CNS) infections and the conditions predisposing to them, hydrocephalus and shunt management, and late post-traumatic vascular and mass lesions.

#### Specific Chapter Sections

*Infection and Risk of Infection* The potential risk of serious CNS infection changes the management of some patients even before an infection occurs. Topics discussed in this section include compound depressed skull fractures, penetrating injuries, basilar skull fractures, cerebrospinal fistulae, and pneumocephalus. CNS infections themselves are then discussed including meningitis, brain abscess and subdural empyema. Because specific management options,

especially antibiotic selection, are frequently subject to change, the general approach to diagnosis and management is emphasized in this section. A section on craniectomy and cranioplasty has also been added in view of the increasing recognition of the effects of these procedures on neurologic recovery.

*Hydrocephalus and Shunts* Hydrocephalus is probably the most difficult common complication to diagnose and manage during the rehabilitation of patients with TBI. Not only is it a challenge to identify which patients will benefit from a shunt, but management often becomes even more complicated after shunting. In order to optimally manage these patients, physicians need to understand the different types of shunts and their physiology, as well as common shunt complications. Programmable shunts and other recent innovations are now routinely available, and offer an opportunity for intervention to improve outcome during rehabilitation without requiring further surgery.

*Vascular and Late Mass Lesions* Although vascular lesions such as post-traumatic aneurysm and carotid cavernous fistula are relatively uncommon, physicians treating patients with TBI need to be aware of these complications in order to recognize and treat them promptly when they do occur. Finally, late mass lesions such as chronic subdural

hematoma and hygroma, late presenting epidural hematoma, and delayed post-traumatic intracerebral hemorrhage are discussed.

## CONDITIONS INVOLVING RISK OF INFECTION

### Skull Fractures and Penetrating Injuries

*Depressed Skull Fractures* Depressed skull fractures are generally considered significant if the fragment is depressed below the inner table of the skull by more than the thickness of the skull (1). Tangential skull radiographic views show these fractures most effectively. Compound depressed skull fractures are distinguished from simple depressed skull fractures by the presence of an overlying open wound or laceration, and are therefore associated with a substantial increased risk of infection. This infection risk includes subdural empyema and brain abscess, which are otherwise uncommon following closed head injury. These compound fractures account for up to 85% of depressed skull fractures (1). Both simple and complex depressed skull fractures are often elevated for cosmetic reasons and in the hope of preventing epilepsy. Compound depressed skull fractures are debrided to reduce the risk of infection. Prophylactic antibiotics are often administered to patients with compound depressed skull fractures, although this remains controversial (2–5).

*Penetrating Injuries* Gunshot wounds confer a high risk of infection for several reasons. In contrast with higher velocity military missile wounds, the bullet is retained inside the skull in about 70% of civilian gunshot wounds. The retained bullet becomes a nidus for infection, and retained bone fragments are an even greater problem increasing the risk of infection by a factor of 10 (6). Focal necrosis of tissue in the path of the bullet is also believed to be crucial in the possible development of brain abscess. For these reasons, surgical debridement has been emphasized. In contrast to cerebrospinal fluid (CSF) rhinorrhea, in which antibiotic prophylaxis remains controversial, 87% of 966 neurosurgeons reported that they use antibiotic prophylaxis in patients with gunshot wounds (7). Post-traumatic brain abscess is most common after missile injury. Other types of penetrating injury also associated with increased infection risk include knife wounds in young adults and accidental trans-orbital accidents in children, such as with pencils or wires.

*Basilar Skull Fractures* The base of the skull is comprised of five bones: the sphenoid, ethmoid (including cribriform plate), frontal, temporal (petrous and squamous), and occipital bones (1). Clues to likely basilar skull fracture include CSF leaks, pneumocephalus, hemotympanum,

Battle's sign (ecchymosis in the mastoid region), hearing impairment, peripheral facial nerve weakness, periorbital ecchymosis, fracture of the frontal sinus, and anosmia (8). Because the dura is closely adherent to the bones of the skull base, basilar fractures are frequently associated with dural tears; the resultant fistulous connection between brain and sinuses or ear provides a possible route of entry for infection. Antibiotic prophylaxis after basilar skull fracture has been controversial. A recent meta-analysis of 12 studies with a total of 1241 patients with basilar skull fracture did not find a statistically significant decrease in meningitis in patients treated with antibiotic prophylaxis (9).

### Cerebrospinal Fluid Fistula

*Cerebrospinal Fluid Rhinorrhea* CSF rhinorrhea is a definite indication of a fistulous tract from the intracranial compartment through the dura and skull base. It is therefore important to determine whether CSF rhinorrhea is present in brain injured patients. CSF rhinorrhea is typically a watery discharge with a salty taste, which does not cause nasal excoriation or stiffen bed linen (10). It may be unilateral, may increase with leaning over or prone positioning, and may be associated with a dull constant headache from low intracranial pressure (10, 11). Differential diagnosis includes vasomotor rhinitis, which is typically bilateral with sneezing and lacrimation, and pseudo-CSF rhinorrhea after surgery in the region of the pericarotid sympathetic plexus (12), with nasal stuffiness and hypersecretion, facial flushing, and absent ipsilateral lacrimation.

Glucose strips or tape are notoriously unreliable for diagnosis of CSF rhinorrhea with false-positive rates as high as 75% (13). Quantitative glucose determinations are somewhat more reliable for clear nasal fluid collected in a test tube, but not reliable when fluid is bloody. The definitive test is the beta-2 transferrin assay, which is sensitive and specific for CSF (14, 15). This form of transferrin is not normally found in serum, tears, saliva, or nasal secretions.

Common fistula sites causing CSF rhinorrhea include the ethmoid/cribriform plate region, posterior frontal sinus, roof of the orbit, and sphenoid sinus regions. When rhinorrhea is unilateral, it accurately predicts the site of the dural tear and fracture in 95% of cases. However, only one-half of patients with bilateral rhinorrhea have bilateral dural tears (1). Fractures are particularly common into the ethmoidal air cells just lateral and posterior to the cribriform plate (Figure 33-1)(10), and injury in this area is characteristically associated with anosmia (1). Rhinorrhea into the ethmoid air cells sometimes stimulates fibroblastic proliferation that may grow to close the underlying defect (10). In contrast, dural tears of the posterior wall of the frontal sinus do not tend to heal, and typically cause persistent rhinorrhea requiring surgery. Frontal sinus fracture can be associated with

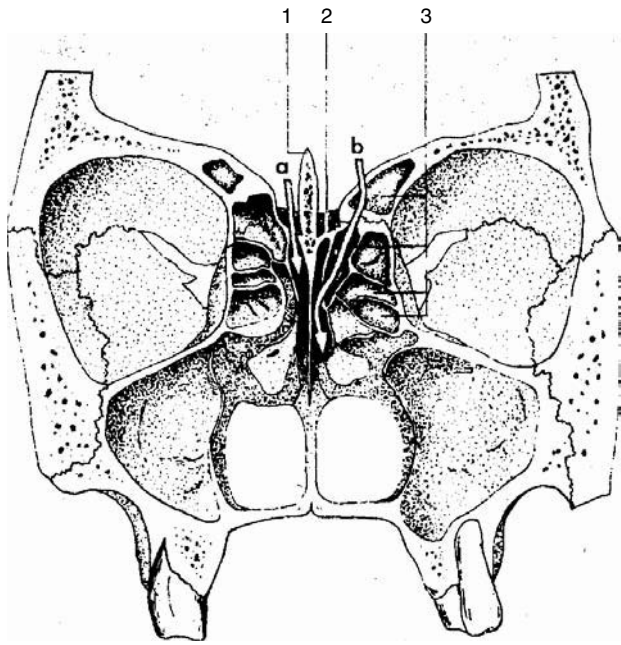


FIGURE 33-1

(a) Fracture in cribriform plate, (b) Fracture through ethmoidal cells, which is the more usual type. (1) crista galli, (2) cribriform plate, (3) ethmoidal cells. (From MacGee EE: Cerebrospinal fluid fistula. In Vinken PT, Bruyn GW (eds): Handbook of Clinical Neurology, vol. 24. New York, Elsevier, 1976, with permission.)

anesthesia of the supraorbital nerves, subconjunctival ecchymosis, palpable depression over the frontal sinus region, and air in the orbit. A leak into the sphenoid sinus is particularly likely to cause profuse rhinorrhea (16).

Several diagnostic techniques are used to localize the site of a CSF leak. Radioisotope cisternography, with radioisotope injected into the CSF and measured in pledgets placed in the nose is not as precise as newer methods for pinpointing the exact location of the leak, but can be useful for lateralization of a slow or intermittent leak (17). Special MRI techniques, using images with heavy T2 weighting may highlight CSF sufficiently to show the leak (17, 18). CT cisternography, with CT scan after injection of a contrast dye, is effective in patients with an active leak but may fail to visualize intermittent leaks, and is an invasive technique. Intrathecal fluorescein with endoscopic visualization has been reported as a very effective means of precisely identifying slow leaks, especially as part of an endoscopic surgical repair procedure (17, 18). Although a high incidence of side effects was initially reported with intrathecal fluorescein, including transient paraparesis and seizures (19), others have used the technique more recently and encountered little difficulty (17, 18).

**CSF Fistula and Meningitis Risk** CSF rhinorrhea implies a 10-fold increase in the risk of subsequent meningitis (20).

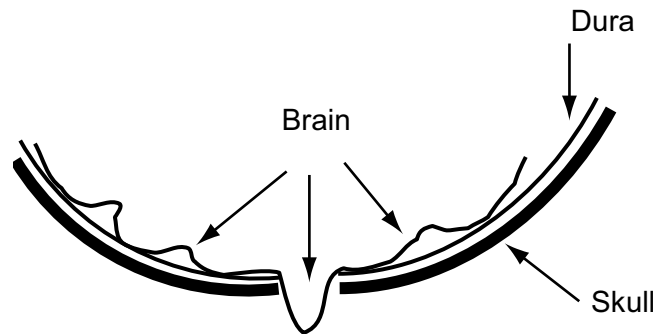


FIGURE 33-2

Fistula with brain tissue protruding through dura and skull. Even in the absence of active CSF fluid leakage, this presents a significant risk for eventual development of meningitis. Over time the plug of brain tissue may shrink somewhat with changes in brain compliance and provide route of entry for infection

However even when rhinorrhea resolves, as it does in 85% of cases within 1 week (21), there is now strong evidence of a very high (30–40% or more) risk of late meningitis (8, 17, 18, 22). In one series of 44 patients with meningitis, over one-half of the episodes occurred more than 1 year after injury (8), and cases have been reported many years later. Such late occurrences of meningitis underscore the importance of taking an aggressive approach to ensure closure of dural tears acutely and of considering a possible fistula when patients with a prior TBI present with meningitis. Rhinorrhea has also presented years after the original trauma in multiple cases (22, 23, 24, 25). Coughing, sneezing, hard work, or inverted posture may facilitate opening of the leak. Computed tomography (CT) or magnetic resonance imaging (MRI) may show evidence of encephalocele (brain protrusion through a skull defect) without clinical signs of basal fracture or CSF leak. In some late presenting cases brain tissue has been trapped in the dural defect, apparently making a temporary seal but preventing dural closure (23) (Figure 33-2). In cases presenting years after the injury the cerebral plug may become inadequate with brain atrophy or change in cerebral compliance.

Endoscopic extracranial techniques can now repair 90% of fistulae without requiring craniotomy (17). This avoids additional brain trauma and often preserves smell, which is typically lost with intracranial repair. Large defects or those associated with mass lesions may still require craniotomy. Lumbar drainage has often been used postoperatively after definitive dural repair, but it is not usually recommended as sole treatment (21, 22, 26).

Although prophylactic antibiotic use in patients with CSF rhinorrhea remains highly controversial, there is more support for prophylaxis in patients with rhinorrhea than in patients with basilar skull fracture alone (1, 9, 10, 20, 27, 28). One meta-analysis study found a statistically significant benefit by pooling studies which showed a

similar trend but individually lacked sufficient numbers to achieve statistical significance (27), while another meta-analysis came to the opposite conclusion (9).

**Cerebrospinal Fluid Otorrhea** Otorrhea occurs when petrous temporal bone fracture and dural tear are combined with tympanic membrane tear. The exact incidence of temporal bone fracture is uncertain since as many as 60% of these fractures may be missed with routine CT imaging (29). However they are believed to constitute over one third of basilar skull fractures (29). Otorrhea has been estimated to occur in approximately 7% of all patients with basilar skull fractures (30), or approximately 20–25% of those with temporal bone fractures (1). Petrous temporal bone fractures are divided into longitudinal and transverse types. Both types are associated with otorrhea. Longitudinal fractures run in the antero-posterior direction and are five times more common. Longitudinal fractures often are associated with torn tympanic membrane, ossicular disruption, and delayed transient impairment of the facial nerve. Transverse fractures run at right angles to the petrous axis and are associated with injury to the inner ear and eighth nerve, and immediate lasting injury to the facial nerve. Unlike CSF rhinorrhea, CSF otorrhea almost always resolves spontaneously in less than 1 week (1, 23). In the few cases that persist, the reported rate of cessation after a single surgical procedure is 98% (1).

**Pneumocephalus** Pneumocephalus is defined as gas within the cranial cavity. In TBI this is usually air, with the exception being gas produced in a brain abscess by anaerobic infection. Air may be present in any of the intracranial compartments, but frontal subdural or intracerebral air were most common in a series of 295 patients (31). Pneumocephalus occurs in 15% of patients with a fistula (22), and concurrent rhinorrhea is reported in 30–50% (31).

Two major mechanisms for posttraumatic pneumocephalus have been proposed, the inverted bottle mechanism and the ball-valve mechanism. Relatively early pneumocephalus in patients with rhinorrhea or otorrhea is consistent with the inverted bottle mechanism. It is similar to what happens when one drinks or pours from a bottle; as CSF escapes from the cranium, eventually air must enter to allow more CSF to exit. On the other hand, in the ball-valve mechanism, air is forced into the cranium with pressure, as by a cough or sneeze, and then cannot exit because the meninges or cerebral tissue tamponades the leak. The delayed build-up of intracranial air from this recurrent one-way valve mechanism fits the peak incidence of pneumocephalus at 1–3 months post injury.

The term “tension pneumocephalus” is used when intracranial air acts as a mass lesion, compressing the



FIGURE 33-3

CT scan showing sizeable right-sided extra-axial pneumocephalus. Patient initially had TBI with subdural hematoma, later hydrocephalus and recurrent right subdural hygroma treated with ventriculoperitoneal shunt and shunt into subdural space on right, followed by subsequent postoperative development of pneumocephalus. In this film, some fluid is now seen inferiorly in the subdural space surrounding the catheter, in addition to the air superiorly. Catheter is also seen entering the right lateral ventricle. Despite the mild mass effect seen, both the subdural air and fluid eventually resolved from this point with conservative management

underlying brain and causing headache, motor paresis, meningeal signs, and even psychosis. Sometimes this type of picture is seen postoperatively, such as after evacuation of a subdural hematoma (Fig. 33-3).

Tension pneumocephalus has been described to present with severe progressive unilateral headache as much as four years after original brain injury (32). Although this late presentation is not common, it underscores the importance of considering this diagnosis in the comprehensive assessment of the post-traumatic headache patient.

One bedside finding, the “bruit hydro-aérique (31),” or cranial succession splash, is pathognomonic for pneumocephalus. It is heard by auscultation of the head during head movement and is sometimes also described subjectively by the patient. Although reported in only 7% of patients with pneumocephalus, it is likely that many examiners have not looked for it.

Definitive treatment for pneumocephalus entails repair of the underlying dural tear and fistula. In some obtunded patients with tension pneumocephalus, the air collection is tapped via a burr hole as an initial temporizing measure (31).

## INFECTIOUS COMPLICATIONS

### Meningitis

*Presentation and Approach to Management* Trauma to the head is the most common cause of meningitis in adults (33). The classical symptoms of meningitis are well known, including headache, fever, stiff neck, and confusion. However, typical features may be lacking in 20% of patients, particularly the very young, the very old, and the immunosuppressed (34). Focal signs are typically absent in meningitis, and their presence warrants obtaining a CT scan to rule out abscess, empyema, or other mass lesion. Lumbar puncture characteristically reveals CSF pleocytosis (predominantly polymorphonuclear cells) with lowered glucose (less than one-third the blood glucose in three fourths of patients). Identification of the causative organism in the cerebrospinal fluid generally guides specific antibiotic selection, along with general principles such as ability of the antibiotic to cross the blood brain barrier, effectiveness in purulent fluid, and ability to exert a bacteriocidal effect (35, 36). Due to the changing development of drug resistant strains, availability of newer antibiotics, and the need for treatment to be tailored to the specifics of each case, only some broad guidelines are offered here, and the reader is advised to check updated resources for best management of each case.

*Common Organisms and Management* Streptococcus pneumoniae are by far the most common causative organisms causing post-traumatic meningitis, accounting for over 80% of some series (33). Whereas penicillin was previously the mainstay of treatment for these pneumococci, with the emergence of resistant strains, the use of third generation cephalosporins (such as cefotaxime, ceftazidime, or ceftriaxone) is now often suggested, sometimes accompanied by vancomycin and rifampin (35). Hemophilis is important in young children, and third generation cephalosporins have also been advocated. (35) Patients with penetrating injuries are more likely to have Staphylococcus aureus or gram-negative meningitis (20). Staphylococcus aureus can be treated with nafcillin or oxacillin, or vancomycin for resistant organisms. Adult meningitis during the first few days after nonpenetrating injury is almost always pneumococcal. Gram-negative infections usually present later, necessitating broader-spectrum coverage in late presenting meningitis. Shunt-related infections warrant special mention, because they often are indolent clinically and usually caused by Staphylococcus epidermidis. Shunt removal is generally necessitated along with vancomycin intravenously, or even intrathecally for refractory cases (see hydrocephalus section for further discussion)(37, 38). Broad spectrum coverage of posttraumatic meningitis with a combination of agents, such as vancomycin plus ceftazidime, can

sometimes be instituted when diagnostic results from cerebrospinal fluid are not available (37).

### Subdural Empyema

*Risk Factors and Presentation* Subdural empyema is most common in males under age 20, and is actually more often secondary to paranasal or ear infections than trauma (16, 20). Post-traumatic subdural empyema is usually secondary to septic compound skull fracture, comprising 77% of a series of 53 cases of post-traumatic subdural empyema. (39) Presentation is acute and fulminant with fever, headache, and obtundation (20). Periorbital swelling (40) or tenderness over the sinuses or mastoid may provide additional clues. Focal signs and seizures are common(16, 34).

*Evaluation and Management* CT scans show an extraaxial collection with medial membrane enhancement (41). MRI scans typically shows low signal on T1-weighted imaging and high signal on T2-weighted images(42). Lumbar puncture is contraindicated. Multiple organisms are usually present, including streptococci. When only one organism is cultured, it is most often Staphylococcus. In addition to appropriate antibiotics, either burr hole drainage or craniotomy is recommended (20, 34, 40, 42, 43). Although success has frequently been reported with burr holes (34, 40), large size, midline shift, parafalcine or posterior fossa location, and loculation have been identified as factors favoring craniotomy (43).

### Brain Abscess

*Risk Factors and Clinical Presentation* Trauma is a less common cause of brain abscess, compared with spread from sinusitis or middle ear infection, or hematogenous spread from pulmonary or dental infection. In fact, only approximately 10% of brain abscesses are secondary to TBI or neurosurgical procedure. Among patients with TBI, brain abscess is three times as likely after gunshot wounds, and eight times as likely with wound complications, such as hematomas, fluid collections, wound infection and cerebrospinal fistula (44). Brain abscess is rarely seen as a complication of basal fracture alone (45). Classically the presentation of brain abscess peaks at about 2–3 weeks after injury, but the mean time of presentation was actually more than 3 months post injury in one series of 36 patients (46). Presentation is frequently with signs of increased intracranial pressure rather than with acute febrile illness. In one series headache was present in 90% and vomiting in 65% (47), while as many as half of patients are afebrile at presentation (45, 47). Focal signs occur in 50–75%, with changes in mental status notable in one half of patients, and seizures in one-third (45). Table 33-1 contrasts key features of meningitis, subdural empyema, and brain abscess.

**TABLE 33-1**  
***Distinguishing Features of Different Types of Intracranial Infection***

	<b>MENINGITIS</b>	<b>SUBDURAL EMPYEMA</b>	<b>BRAIN ABSCESS</b>	<b>SHUNT INFECTION</b>
Predisposing condition	Basal fistula	Penetrating injury, Compound depressed fracture, Paranasal sinus/ear	Penetrating injury, Compound depressed fracture, Paranasal sinus/ear, Hematogenous	Recent shunt or shunt revision (70% within 2 months)
Organisms	<i>Pneumococci</i> (early) Gram negatives (late) <i>Staphylococci</i> (late)	Mixed/ <i>Streptococci</i> <i>Staphylococci</i> Gram negatives	Polymicrobial/ anaerobic <i>Staphylococci</i>	<i>Staphylococcus epidermidis</i>
Presentation	Acute Headache, nuchal rigidity, mental status change	Acute fulminant Periorbital swelling Sinus tenderness Increased ICP, Seizures, focal signs	Subacute/ progressive Increased ICP Focal signs	Indolent Malaise, nausea irritability
Fever	Yes	Yes	Only 50%	Low-grade
WBC	Elevated	Elevated	Often normal	Often normal
CT/MRI	Negative or meningeal enhancement	Extra-axial – medial rim enhancement	Intra-axial ring enhancement, especially late; MRI T2 capsule low signal	Often nondiagnostic
Lumbar puncture	Increased WBC, decreased glucose	Contraindicated (Increased WBC, normal glucose)	Contraindicated (Often negative)	LP not reliable Must tap shunt for diagnosis
Management	Antibiotics	Antibiotics Burr hole/craniotomy	Antibiotics Debridement Stereotaxic aspiration	Antibiotics, Steroids Remove shunt

Key: ICP = intracranial pressure, WBC = white blood count, LP = lumbar puncture.

**Abscess Stages and Imaging** Stages of abscess formation have been recognized pathologically and correlated with CT and MRI scan findings (45). Early on the term cerebritis is used because of the presence of inflammatory cells in a perivascular location. CT scan at this stage shows low density with little enhancement, which may be solid. MRI during cerebritis is more sensitive (34) and shows uniform signal with indistinct margins (47). Later in cerebritis both the necrotic center and surrounding edema may reach maximal size, fibroblasts and macrophages are found at the periphery, and CT scan may show a thin rim of enhancement and increasing edema. Next a capsule of collagen and reticulin begins to develop; this forms more slowly on the ventricular side of the abscess. CT scan now shows a ring-enhancing capsule (less medially) and a low-density center. MRI scan shows the capsule as low signal on T2-weighted images (47). Diffusion weighted MRI has been effective in distinguishing brain abscess from other mass lesions, such as brain tumors. On diffusion weighted MRI the central core of a brain abscess is hyperintense, whereas tumors such as glioblastoma or metastasis are typically hypointense centrally (48).

**Organisms and Treatment** Most brain abscesses are polymicrobial and include anaerobes. Gas on CT scan

may help in early differentiation from tumor and suggests anaerobic organisms. Staphylococci are found in about 10% of brain abscesses and are more frequent after trauma (45). Lumbar puncture is contraindicated in brain abscess and usually not diagnostically helpful if performed inadvertently. Therefore, choice of antibiotic reflects the anticipated polymicrobial etiology supplemented by information from aspiration of the abscess. For example, in the absence of specific culture information, a combination of a third generation cephalosporin, nafcillin or vancomycin for Staph, and metronidazole for anaerobes might be utilized. As an abscess heals, the capsule becomes more isodense on serial CT scans. Steroids are frequently used effectively in brain abscess to decrease edema, but may delay encapsulation of the abscess and make monitoring of response to therapy more difficult. Surgical management of brain abscess includes excision or CT-guided stereotactic aspiration (49, 50). Indications to the stereotactic approach include surgically inaccessible location, cerebritis stage, or poor neurologic or general medical condition. Excision is useful for removal of foreign material and necessary for posterior fossa lesions. Adverse prognostic factors in brain abscess include young or old age; large, deep abscess; coma; or rupture into the ventricular system. Mortality from brain abscess in

Vietnam was 54%, and survival was worse with gram-negative organisms. However, good recovery can occur, and 30% or less of survivors are reported to have significant residual hemiparesis.

## CRANIECTOMY AND CRANIOPLASTY

### Craniectomy and Cranioplasty

*Role of Cranioplasty in the Recovery Process* Craniectomy (skull flap left out) is performed acutely in many patients with either uncontrollable intracranial pressure or with penetrating or contaminated wounds. Traditionally cranioplasty (replacement of bone flap or prosthesis) was often delayed six months or longer to minimize risks of infection or complication (16, 51, 52), and the procedure was considered more cosmetic and protective than therapeutic. However, it now appears that many patients with craniectomy develop the so called “syndrome of the trephined” (53), and can show considerable neurologic and functional improvement with early performance of cranioplasty. The deficits shown to improve upon performance of cranioplasty have included headaches, apathy, hemiparesis (54), midbrain syndrome with eye movement disorder (55), tremor, gait, and cognitive function (53). Patients exhibiting the syndrome of the trephined have been described to show the “sinking skin flap syndrome”, where the craniectomy flap tends to be markedly ingoing (53). This is particularly likely to occur in patients with concurrent shunts for hydrocephalus (56), and because craniectomy changes the brain compliance it may actually play a role in inducing hydrocephalus (53, 56).

In those patients where marked clinical improvement occurs with cranioplasty, the improvement has correlated with cerebral blood flow improvements of up to 30% as well as improved distribution of flow. Based upon measurements of transcranial cerebral oximetry and of ratios of phosphocreatine to inorganic phosphate (sensitive to rate of oxygen depletion), it has been suggested that cranioplasty induces more energy efficient mitochondrial function (53). The practical impact of these studies is the desirability of performing cranioplasty earlier, particularly in patients with markedly ingoing skull defects or ventriculoperitoneal shunts.

*Cranioplasty Alternatives* Cranioplasty can be performed with the patient’s own bone flap, which can be frozen and stored (57), or stored in the patient’s abdomen (58). Alternatively multiple materials can be used to create a cranioplasty flap, including titanium mesh (59), hydroxyapatite, and polymethylmethacrylate (60), and computerized techniques can be used to generate a custom made cranioplasty prosthesis (61). For patients with shunts and depressed skull flaps, it has been suggested to clip the shunt

temporarily to reexpand the brain prior to cranioplasty to minimize dead space at the time of surgery (62).

## HYDROCEPHALUS

### Overview

*Importance After TBI* Hydrocephalus is the most common treatable neurosurgical complication during rehabilitation of traumatic brain injury (TBI)(63), and its treatment can sometimes have a dramatic impact on rehabilitation and outcome. One recent study estimated an incidence of post-traumatic hydrocephalus at 45% in patients with severe TBI (64). However, differentiation of dynamic hydrocephalus from central atrophy or ex vacuo ventricular dilation remains problematic(65), and the physiology relevant to the decision process in managing these patients is complex. Practical management after a shunt includes prevention and treatment of other complications such as overdrainage and subdural hematoma, and the introduction of programmable shunts now offers additional opportunity for the physician to intervene medically during rehabilitation. Therefore the pathophysiology and clinical presentation of hydrocephalus, noninvasive and invasive diagnostic studies, shunt types including newer valve innovations, and shunt complications will be reviewed in some detail.

*Types and Variants* Hydrocephalus is divided into communicating and noncommunicating types(66). In communicating hydrocephalus, the different portions of the ventricular system are interconnected, and fluid may exit the ventricular system freely to the cisterns and subarachnoid space, whereas in noncommunicating (obstructive) hydrocephalus CSF flow is obstructed either between the ventricles or in exiting the ventricular system.

Post-traumatic hydrocephalus is communicating in the vast majority of cases, and enlargement characteristically involves all components of the ventricular system. Blood products, protein, or fibrosis typically interfere with circulation of cerebrospinal fluid and its absorption into the bloodstream through the arachnoid granulations (67).

When only selected portions of the ventricular system are enlarged, noncommunicating hydrocephalus should be considered. For example, large lateral and third ventricles with a small fourth ventricle in a patient with a large head circumference is generally attributable to aqueductal stenosis (66, 68), a congenital condition which may become decompensated by TBI. Lumbar puncture is contraindicated in these patients. Endoscopic third ventriculostomy can effectively bypass the aqueductal obstruction without requiring a shunt in some cases (69). The procedure involves placing hole in the floor of the 3rd ventricle creating a connection with the adjacent cistern.



Focal ventricular enlargement frequently occurs on an atrophic or porencephalic basis in brain areas that have sustained known damage. Less often, trapping of an isolated portion of the ventricular system may produce focal enlargement with signs of increased intracranial pressure or focal deficits (70–73). Occasional cases of multiloculated hydrocephalus are encountered, usually secondary to meningitis, ventriculitis, or intraventricular hemorrhage (74). The multiple irregular intraventricular septations of the enlarged ventricular system can be effectively treated with fenestration by intraventricular endoscopy (74–76).

### Pathophysiology of Chronic Communicating Hydrocephalus Including Normal Pressure Hydrocephalus (NPH)

**Pascal's Law** Pascal's law of hydraulic systems states that  $F = P \times A$ , where  $F$  is the force against the ventricular wall,  $P$  is the intraventricular pressure, and  $A$  is the area of the ventricular wall (77). This formula implies that when the area of the ventricular wall is large, a substantial expanding force may be generated from within the ventricle without the necessity of high pressure. For example, if a certain degree of ventricular enlargement initially results from increased pressure, ongoing enlargement may take place, even though pressures are no longer elevated (78).

**Decreased Parenchymal Pressure and Compliance** Rather than the absolute intraventricular pressure, the difference between the intraventricular pressure and that of the surrounding tissue determines ventricular size (77, 79). This concept may be understood more clearly by considering that the size of a balloon is determined not only by the pressure inside the balloon, but by the pressure of the air inside relative to the air outside the balloon. Changes in the viscoelastic properties of brain parenchyma with related decrease in parenchymal pressure therefore probably contribute significantly to the development of hydrocephalus, since it is the difference between cerebrospinal fluid pressure and intraparenchymal pressure which determines ventricular size (80). A gradient of reduced blood flow has been documented in the periventricular white matter of patients with NPH, as well as altered blood flow autoregulation which likely contributes to watershed ischemia (81). Damage to myelin and axons has also been described when hydrocephalus is longstanding (82). These factors are probably among those that contribute to the decreased elasticity or compliance of the brain parenchyma which is felt to be important in the development of NPH.

**Pulsatile CSF Flow** Disturbances of pulsatile CSF flow may be more important than blockage of CSF absorption in causing chronic communicating hydrocephalus (83). According to the Monro-Kellie doctrine, the volume of

the intracranial contents including brain, blood, and CSF is constant (84). This means that arterial blood inflow during systole is accompanied by both outflow of venous blood and shifting of CSF into the spinal compartment (84). Furthermore CSF movement is not simple unidirectional flow but complex, and the basal cisterns probably play an important role in dynamic compliance. When intracranial compliance is decreased, restricted arterial pulsation and increased pulse pressure in brain capillaries have been postulated to play a causative role in chronic hydrocephalus (85).

### Clinical Presentation of Hydrocephalus

**Acute Hydrocephalus** Early post injury acute hydrocephalus can present with symptoms of increased intracranial pressure including headache, nausea, vomiting, and lethargy or decreasing mental status. Associated signs can include a tense bulging craniectomy flap, papilledema, and Cushing's triad of hypertension, bradycardia, and hypoventilation.

**Normal-Pressure Hydrocephalus** NPH is well known to present with the clinical triad of dementia, gait ataxia, and urinary incontinence. Of the three, gait impairment is the most important diagnostically and most likely to respond to shunting. The classic gait disturbance is short stepping, wide based, with a "magnetic" difficulty in lifting the feet, and characteristic of frontal or subcortical rather than cerebellar dysfunction (86, 87). The cognitive difficulties in NPH are apt to include long latency responses, decreased attention, and poor initiation rather than deficits such as aphasia or agnosia. In patients with TBI, the presentation of hydrocephalus is not limited to the classic triad of normal pressure hydrocephalus, and should be considered in any patient who worsens or fails to progress adequately. A prefrontal syndrome (88) or akinetic mutism are additional clinical syndromes that should particularly raise suspicion for hydrocephalus. Patients with meningitis or intracranial hemorrhage, especially subarachnoid or intraventricular hemorrhage, are particularly at risk for development of hydrocephalus.

### Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

**Ventriculomegaly** CT and MRI scans have been invaluable in providing information about ventriculomegaly, and multiple methods have been devised for measuring ventricular size, calculating ventricle to brain ratios, and assessing shunt function (89–93). However, ventricular size alone has not been a reliable predictor of whether a patient has shunt responsive hydrocephalus rather than cerebral atrophy (94). In fact, ventriculomegaly has been reported in as many as 72% of patients with severe TBI (95), and it is now recognized that the extent of

ventriculomegaly can be correlated with severity of diffuse axonal injury and outcome, complicating assessment for hydrocephalus in patients already known to have severe TBI (96–98). Ventricular configurations favoring dynamic hydrocephalus include enlargement of temporal horns, convex shape of the frontal horns, widening of the frontal horn radius, and frontal horn location closer to midline narrowing the “ventricular angle” (70).

**Sulcal Absence and Periventricular Lucency** Ex-vacuo ventricular dilatation or cerebral atrophy typically involves sulcal prominence. Small or absent sulci on a CT scan in combination with ventriculomegaly are predictors of a good response to shunting, although the presence of sulci does not preclude a positive response (94). Periventricular lucency has been a valuable predictor of a good response to shunting, especially when lucencies have been seen in multiple periventricular locations (see Figure 33-4) (94, 99). In hydrocephalus, fluid seeps across the ependymal lining of the ventricle and causes interstitial edema. This transependymal fluid is seen as lucency on CT and as smooth increased T2 signal on MRI. Contusion, infarction, or demyelination in the periventricular white matter can be difficult to distinguish from transependymal fluid, but are usually more irregular and asymmetric (100).

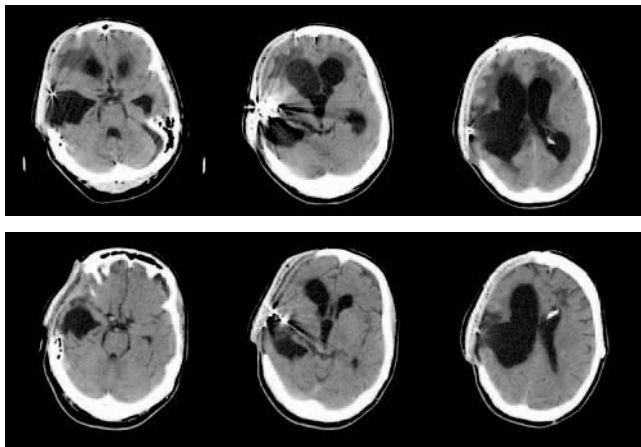


FIGURE 33-4

Hydrocephalus pre- and post shunting. In the pre-shunt scans (top) note marked periventricular lucency in the white matter consistent with transependymal fluid in addition to ventricular enlargement. There is also artifact from aneurysm clip and right hemispheric encephalomalacia, maximal in the right temporal lobe. Post shunt scans show persisting encephalomalacia of the right hemisphere including the right lateral ventricle and right temporal horn. Shunt is now seen entering the left lateral ventricle which has now normalized (including left temporal horn), and periventricular lucency has largely resolved. Surprisingly a CSF tap test (see text) had actually been negative in this patient, but after performance of ventriculoperitoneal shunt there was nonetheless marked clinical improvement

**Additional MRI Findings** MRI provides more anatomic detail about the configuration of the ventricular system than CT, including imaging of structures such as the Sylvian aqueduct and foramen of Monro. More rapid flow through the Sylvian aqueduct can be detected as decreased signal or “flow void” in the aqueduct in patients with hydrocephalus due to decreased compliance of the ventricular wall of the 3rd ventricle during systole (70, 101, 102). A series of linear measurements on MRI, essentially reflecting size and configuration of the third ventricle, can be used to distinguish obstructive hydrocephalus from atrophy, but the effectiveness of this approach in chronic communicating hydrocephalus in TBI has not been assessed (103).

**SPECT Scans** SPECT scans may be helpful in differentiating hydrocephalus from atrophy (64). Subcortical low flow improved in follow up SPECT after shunting in 10 of 11 patients who improved clinically but did not in 3 clinically unimproved patients (104). In a series of eight patients showing clinical improvement after a shunt, a “high percentage” showed improvement of previous temporal lobe hypoperfusion (64).

### Invasive Testing

**Cisternography** Radioisotope cisternography had long been a mainstay in the diagnosis of hydrocephalus. After lumbar injection of radioisotope, pooling in the ventricles rather than progression of uptake over the convexity was taken as indicative of normal pressure hydrocephalus. However, cisternogram findings may really be more of a dilution and concentration process than a true measurement of CSF flow (84), and cisternography does not improve the diagnostic accuracy of combined clinical and CT criteria (105). Cisternography based predictions were the same in 43% of patients, better in 24%, and worse in 33% (105).

**Lumbar Infusion Studies** Infusion of fluid via a lumbar or ventricular catheter with measurement of drainage at designated pressures allows calculation of the outflow resistance, a measure of the difficulty of CSF absorption (94). If the outflow resistance is low, significant volumes of CSF can be readily absorbed and a shunt is not likely to help. On the other hand, increased outflow resistance means CSF is not readily absorbed. It is related to decreased compliance of the system, and is predictive of a positive response to shunting (68, 94, 106–110). Of interest, ventricular size does not correlate well with either outflow resistance or response to shunting (84, 106). Infusion studies have relatively low risk compared with the long-term morbidity of a shunt (107, 108). Unfortunately, despite their reported value and frequent use in Europe, these studies are infrequently performed in many U.S. hospitals. The suggestion of a one-stage “test and shunt if needed” procedure may make infusion studies more practicable (68).

**CSF Tap Test and CSF Drainage Trial** A lumbar puncture with the removal of 50 ml of CSF has been widely advocated as a CSF tap test (99, 103, 112–116). If the patient shows an improvement in neurologic status after lumbar puncture, the test is viewed as positive. However, a lack of response does not preclude response to a shunt, because shunting produces more sustained ventricular decompression (67, 86). Therefore, the CSF tap test is most useful to identify patients who otherwise might not be shunted; a strong candidate would be shunted even in the face of a negative tap test. A more prolonged CSF drainage trial with a spinal catheter for 3 to 5 days has been shown to have both greater sensitivity and predictive value of shunt success than a simple tap test alone. (111, 112).

**Combined Studies** A recent patient series had both lumbar infusion testing and CSF tap tests (114). The two tests agreed in only 45% of patients, with use of both tests recommended, since each test identified patients missed by the other test. When the tap test was positive, 94% of patients had a good response to shunting, but if the test were used alone, 58% of positive shunt responders would have been missed. The lumbar infusion test was only 80% predictive of success, but false negatives were 16%. In another series, perfusion weighted MRI or SPECT were performed before and 1 day after CSF tap tests (115). Nine patients were both clinically improved and had improved blood flow after the tap, and all responded well to shunting. In addition, six patients who were not clinically improved by the tap test, but did have improved

blood flow on perfusion weighted MRI or SPECT after the tap test also showed good response to shunting.

### Approach to Shunt Decision Making.

**Establishing the Diagnosis and Therapeutic Expectations** Table 33-2 reviews multiple considerations relevant to identifying dynamic hydrocephalus. The combination of the clinical course and findings, CT and MRI appearance, and in some cases SPECT and CSF tap test (and lumbar infusion testing if available) may help establish the diagnosis. Patients with TBI are likely to show only a partial response to shunting, because deficits from hydrocephalus are superimposed on deficits from the original TBI. This should be clearly explained to family members before pursuing shunting, to prevent or minimize any unrealistic expectations. However, given the potential significant benefit to patient outcome, an aggressive approach to identification and treatment of hydrocephalus is warranted for the severe TBI patient.

### Treatment

**Treatment Without a Shunt** The definitive treatment of hydrocephalus is surgical, usually the placement of a shunt. Treatment with carbonic anhydrase inhibitors, such as acetazolamide or furosemide (116), or with serial lumbar punctures is only a temporizing measure. Similarly, external ventricular drainage may be used on a temporary basis, particularly for obstructive mass effect or

**TABLE 33-2**  
*Factors Distinguishing Dynamic Hydrocephalus from Ex Vacuo Ventricular Dilatation*

FEATURE OR TEST	DYNAMIC HYDROCEPHALUS	EX VACUO VENTRICULAR DILATATION
Antecedent history	Hemorrhage, esp IVH or SAH	Anoxia or diffuse axonal injury
Clinical deficits	NPH triad (dementia, gait impair, urinary incontinence), pretectal syndrome (loss of upgaze), akinetic mutism	Consistent with location and severity of injury
Clinical course	Worsening, intermittent, or static	Chronic slow improvement
Skull flap (craniectomy)	Bulging (increased ICP) or increasing prominence	Depressed, ingoing
Ventriculomegaly pattern	Temporal horns, 3rd ventricle, convex frontal horns	Diffuse enlargement, porencephalic dilatation in areas of focal injury
Sulci, fissures, cisterns	Decreased	Increased
Periventricular abnormality	Smooth periventricular signal on T2 MR or lucency on CT (transependymal fluid)	Absent, or frontal contusions or periventricular infarct
SPECT	Periventricular low flow	Normal or Alzheimer's pattern
CSF tap test	Positive or no response	No response
Lumbar/ventricular infusion studies	Increased outflow resistance (poor CSF absorption)	Normal (lower) outflow resistance (good CSF absorption)

Key: IVH = intraventricular hemorrhage, SAH = subarachnoid hemorrhage, NPH = normal pressure hydrocephalus, ICP = intracranial pressure, CSF = cerebrospinal fluid.

while excessive blood products are likely to clog a shunt, but conversion to a shunt is needed for treatment of persisting hydrocephalus. Third ventriculostomy, where a connection is endoscopically created between the floor of the third ventricle and the underlying cistern, is the one exception of a definitive treatment for hydrocephalus not requiring placement of a shunt. It is most commonly used to treat aqueductal stenosis (117), where the procedure can bypass the obstruction at the Sylvian aqueduct (83). More recently there has been renewed interest in the procedure for other forms of hydrocephalus as well, mainly because of the potential to improve intracranial compliance without diverting fluid from the CSF compartment (85, 118).

**Shunt Types** Ventriculoperitoneal shunts are used most commonly for post-traumatic hydrocephalus, but ventriculoatrial, ventriculopleural, and lumboperitoneal shunts are useful in certain circumstances. Ventriculoatrial shunts are used more frequently in children with obstructive hydrocephalus. Occasionally ventriculopleural shunts may be substituted in cases with abdominal infection, very high CSF protein, or rarely to drain very low pressure hydrocephalus to the negative pressure of the pleural space (119). Ventriculopleural shunts characteristically cause a small pleural effusion that disappears with shunt malfunction (66). Pleural shunts are avoided in younger children because of the likelihood of symptomatic hydrothorax with a smaller pleural cavity (75). Lumboperitoneal shunts are not commonly seen, but can be used for communicating but not obstructive forms of hydrocephalus. Lumboperitoneal shunts have also been used for pseudotumor cerebri, when ventriculoperitoneal shunt placement may be difficult because of small ventricular size (66). Placement of a lumboperitoneal shunt often obliterates the basal cisterns on CT scan of the head, and the return of previously obliterated cisterns is a reliable indicator of shunt malfunction (120). Although usually asymptomatic, cerebellar tonsillar herniation (iatrogenic Chiari malformation) has been described in as many as 70% of patients with lumboperitoneal shunts (121).

**Shunt Valves and Components** The basic components of a ventriculoperitoneal shunt are the ventricular catheter, valve, and distal tubing. A reservoir may be added proximal to the valve to facilitate access to the ventricular system. Virtually all shunt systems have some type of one-way valve to allow forward flow down the shunt when the pressure gradient exceeds a threshold range and to prevent back flow from the peritoneum. Therapy staff often ask whether a shunt contraindicates inverted position; because of the one-way valve, this is not a problem. Detailed diagrams on a variety of different past and present valve systems and components are available (122). Basic valve types include slit valves, cruciate valves, mitre valves, diaphragm valves,

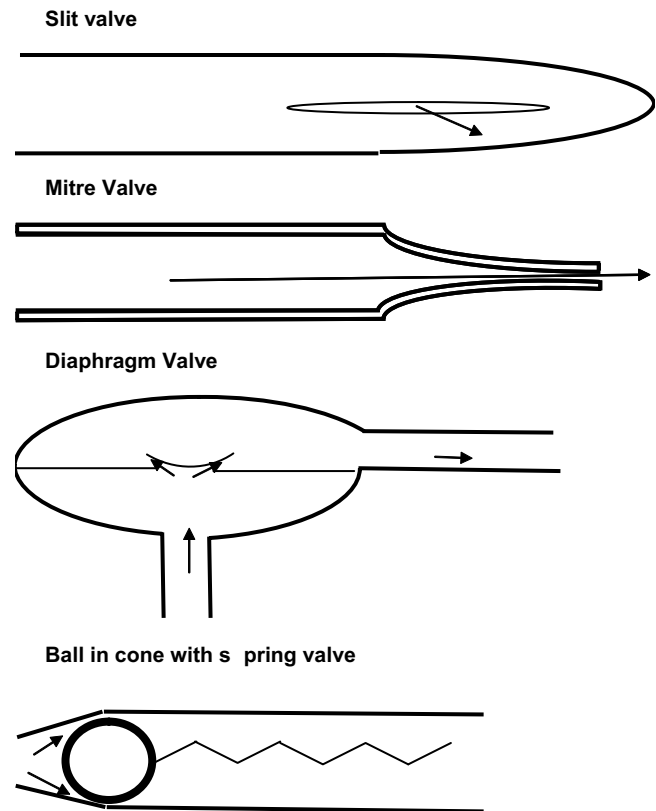


FIGURE 33-5

Common shunt valve types

and ball/spring valves (see Figure 33-5) (122–124). Slit valves open and allow CSF flow when sufficient pressure develops within the tubing; setting is determined by tube thickness. Cruciate valves are similar but have two perpendicular slits instead of one horizontal slit.

Sometimes two slit or cruciate valves are housed in one unit with a pumping chamber between them. Although most shunt systems feature a valve mechanism located over the skull, it is also possible to have a slit valve in the distal tubing instead. The leaflets of a mitre valve act as springs to regulate CSF flow (123). Diaphragm valves allow movement of a diaphragm from its seat or pin as determined by CSF pressure. Reservoirs or flushing chambers are added to many shunt systems. They allow manual pumping of the shunt and potential access to sample CSF or to inject into the shunt system. It is important to know the specifics of a shunt system before injecting into it, because some shunt components (especially older components such as the Spitz-Holter valve, Coe-Schulte second bubble, or Hakim-Cordis valve) may be damaged by needle perforations (125). Most modern shunts, however, have a portion that can be injected without damage. Flushing chambers may be of either single bubble or double-bubble design (see Figure 33-6). If the chamber is proximal to all valves, compression of a

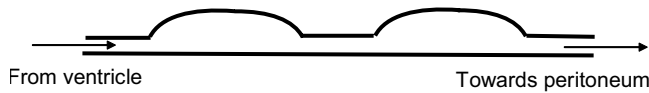


FIGURE 33-6

Double bubble reservoir

single bubble may send fluid both down the shunt and back into the ventricle. If the chamber is between valves, compression may push fluid only in the forward direction. Compression of the distal bubble of a double-bubble shunt after occluding the proximal bubble may also force fluid in the forward direction. A similar result may be obtained in some single-chamber devices by occlusive digital compression of areas of proximal tubing before compression of the flushing chamber. Alternatively, compression of distal bubble or tubing before digital compression of the proximal chamber may force retrograde flow into the ventricle (e.g., intrathecal administration of antibiotics). Of course, access to the ventricle is possible only when a chamber is proximal to all valves.

Shunt valves are also specified by the approximate pressure necessary for opening and forwarding CSF flow, and are commonly divided into low, medium, and high pressure valves (122, 123). Such valve settings are approximate and function differently depending on the compliance of the ventricular system, especially given that CSF flow is pulsatile in nature (126). In general, because of Pascal's law ( $F = P \times A$ ), larger ventricles require a lower pressure for adequate decompression (86). However, valve pressure settings have poor correlation with actual intracranial pressure, which also varies widely among patients with the same valve, and within the same patient with different head of bed positioning (127). When patients do not respond to a shunt, conversion to a shunt of lower pressure occasionally results in clinical improvement (128). Because of the obvious undesirability of reoperation to place a valve with a different pressure, programmable valves have been developed which allow changing the effective opening pressure of the valve noninvasively at the bedside with an external magnet (see further discussion below).

### Shunt Complications

**Frequency of Shunt Complications** The overall incidence of shunt complications is high. Shunt complications include shunt failure, infection, seizures, subdural hematoma, and overdrainage. In 356 adult patients over an 18-year interval, the incidence of revision was 29% (129). In a series of 1,179 patients shunted for hydrocephalus (only 312 patients over age 5 years), the probability of shunt malfunction after 12 years was 81% (130).

**Shunt Failure** Shunt failure may present with irritability, confusion, lethargy, and headache unrelieved by position change. However, shunt failure may also present in a more fulminant manner than the original hydrocephalus, requiring prompt treatment (131). Proximal occlusion of the ventricular catheter is the most common source of blockage, usually accounting for at least 30% of cases of shunt dysfunction (131). Ventricular overdrainage may predispose to proximal occlusion by abutting the catheter tip against the ventricular wall (130). Distal shunt obstruction can be caused by encystment and loculation of the peritoneal contents around the distal catheter tip (72, 75). Abdominal pain, palpable pseudocyst, and ultrasound or abdominal CT may establish the diagnosis. Disconnections of shunt components have accounted for as much as 15% of shunt revisions and often are shown by a shunt series of plain radiographs (132).

Bedside palpation of the shunt sometimes gives a clue to shunt malfunction; excessive resistance to digital compression of the shunt chamber suggests possible distal occlusion, whereas inadequate refill suggests proximal occlusion. Unfortunately, palpation was neither sensitive nor reliable for determining shunt malfunction in a consecutive series of 200 patients (133). CT scans are helpful in demonstrating increase in ventricular size in many cases of shunt malfunction.

Definitive information about shunt blockage can be obtained by performing a shuntogram, where a needle is inserted into the safely perforable portion of the shunt, a pressure recording is done, and the progression of isotope or contrast is followed down the catheter and into the peritoneum (134, 135). With distal obstruction, pressure may be elevated with rapid ventricular filling but lack of distal flow. With proximal occlusion, the distal catheter fills, but pressure is low with slow disappearance of tracer and lack of ventricular filling (135).

**Shunt Infection** Shunt infection has been described in 7–29% of cases. Most infections are acquired at the time of surgery, and 70% present within the first 2 months (136). *Staphylococcus epidermidis* is most common, accounting for approximately one-half of infections, followed by *Staphylococcus aureus* and gram-negative organisms (137). Presentation is typically insidious with low-grade fever, malaise, irritability, and nausea; meningeal irritation is usually not present (137, 138). Erythema over the shunt site, however, is a highly specific sign (136–138).

Diagnosis should be established by performing a shunt tap, not by doing a lumbar puncture. Tapping the shunt leads to accurate diagnosis in 95% of cases, whereas lumbar puncture is positive in only 7–26% of cases (136). Diagnosis is based on culture results, because CSF protein and glucose may be normal and cell count may not be much greater with shunt infection than with shunt alone.

Treatment needs to be individualized to the clinical situation, but in general, the highest overall response rate (96%) has been reported with shunt removal or externalization combined with antibiotics (136). Staph epidermidis is the most common organism causing shunt infection, and sometimes can be difficult to eradicate; intravenous vancomycin, intrathecal vancomycin or a regimen of both vancomycin and rifampin are sometimes used (139).

**Seizures** The prevalence of seizures after shunting has ranged from 5–48% (72), but in patients with posttraumatic hydrocephalus seizures may also result from the original TBI.

**Overdrainage** Overdrainage by shunts is a major clinical problem, causing acute and chronic clinical symptoms, and fostering both proximal shunt obstruction and development of postoperative subdural collections. It has been the driving force behind the development of antisiphon devices, programmable valves, and gravitational shunts. Intraventricular pressure normally becomes slightly subatmospheric when we stand. However, after placement of a shunt, orthostatic intraventricular pressure becomes markedly low (124), reflecting the additional negative hydrostatic pressure from the distal tubing (Figure 33-7). This may cause excessive siphoning of CSF and a low pressure syndrome of orthostatic headache, dizziness, nausea and vomiting, lethargy, and diplopia (131, 140–142).

Some patients with chronically overdraining shunts develop the slit-ventricle syndrome (131, 140, 141). Such patients develop severe nonpostural headaches in the face of persistently small ventricles. Slight increase in ventricular size at the time of clinical symptoms and sluggish shunt refill suggest intermittent proximal shunt malfunction with ventricular collapse against the catheter. Such symptoms develop an average of 4.5 years after shunting and are analogous to pseudotumor cerebri in the tendency toward elevated pressures with small stiff ventricles (140, 141).

**Chronic Subdural Hematoma** Chronic subdural hematomas and hygromas are recognized complications of shunting, occurring in 4.5–28% of patients, and are particularly likely when ventricles are extremely large preoperatively (72). Normally intracranial pulsatile flow and upright posture both shift CSF within the cranium and to the lumbar region, but CSF remains within the CSF compartment; however with shunting CSF exits to the peritoneum, and this can result in an underfilled CSF compartment (84, 118). Since the volume in the cranium is fixed, a loss of fluid in the ventricular compartment may result in creation of increased potential subdural space leading to development of subdural hygroma and hematoma (142, 143). Furthermore, with upright posture, low intraventricular pressures caused by standing are thought to predispose to tearing and leakage from bridging veins. The occurrence of subdural hematoma may require tying off the shunt or turning up the valve

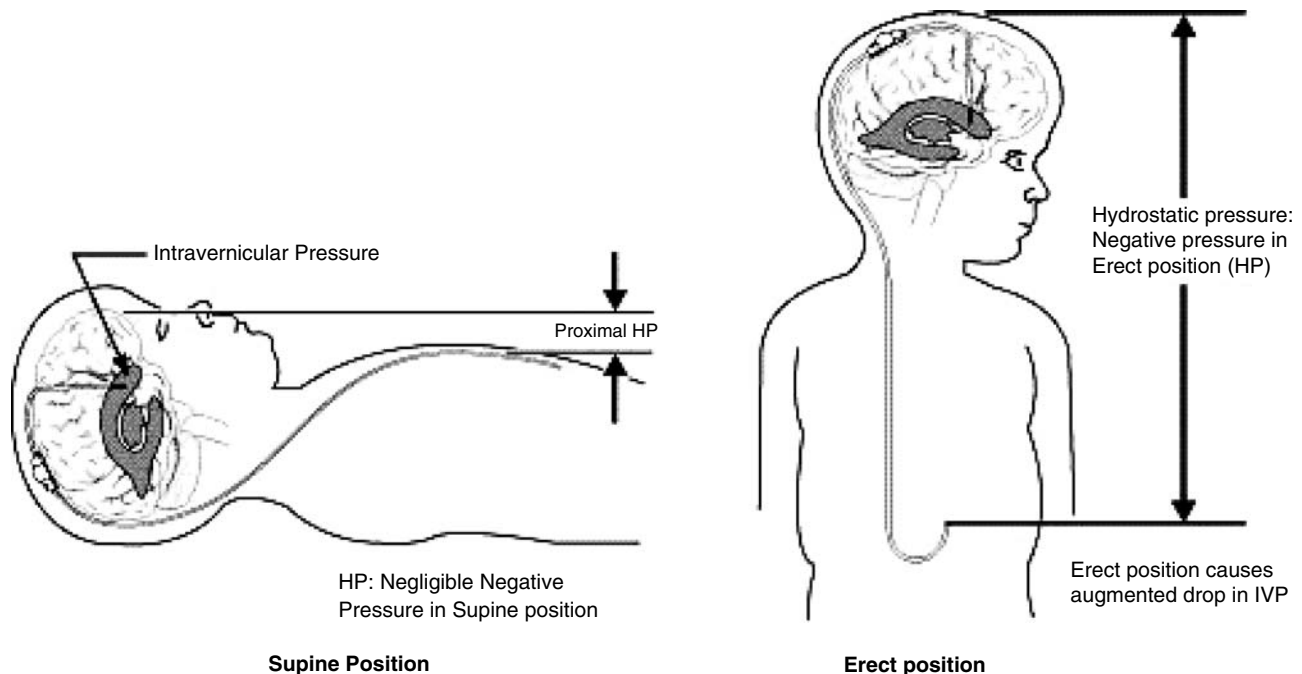


FIGURE 33-7

Positional changes in hydrostatic pressure

pressure setting if the patient has a programmable valve (72, 86, 143). Not all subdural collections are clinically significant; with MRI even very small fluid collections can be imaged (70). Post shunt meningeal fibrosis, with collagenous material in the subdural space, is distinguished from subdural fluid by its dramatic enhancement with gadolinium (70).

### Antisiphon Devices, Programmable Valves, and Gravitational Valves

**Antisiphon Devices** Problems related to overdrainage have led to the development of several special shunt components. Antisiphon devices have been developed with diaphragms that close to counteract negative standing hydrostatic pressures (124, 144). Successful prevention of the dramatic negative standing intracranial pressure has been documented (145). A less useful device is the valve with an on/off occluder bubble following the flushing chamber. Originally designed in hopes of preventing subdural development by transient occlusion, it is not used frequently today. Fortunately palpation or radiographs can determine whether the occluder has inadvertently been compressed (124). Several newer valves have been designed to assist with CSF overdrainage. The Orbis-sigma valve is a flow regulated valve, with variable resistance with three stages of flow. It initially functions like a standard low pressure valve but shows increased resistance with larger flow rates; it also has a decreased resistance safety valve to deal with higher pressures. The delta valve is similar to an antisiphon device in combination with a standard valve, but has been engineered to minimize the area of the valve diaphragm responsive to pressure effects of fluid in the distal tubing. This design was intended to increase physiologic resistance to flow in the upright position selectively (146).

**Programmable Valves** A revolutionary development in shunting for hydrocephalus has been the development of programmable valves which can have their opening pressure changed at the bedside by use of an external magnet (83, 122, 147–153). The Codman Hakim and PS Medical Strata valves (see Figure 33-8) are available in the USA, and the Sophy valve is also available in Europe.

The opening pressure of the Codman Hakim valve can be adjusted in increments of 10 mm H<sub>2</sub>O anywhere from 30 to 200, using a small bedside electromagnet. The Codman Hakim valve has a ruby ball and spring mechanism; the valve's spring tension is controlled by rotation of its spiral Cam with steps, which can in turn be adjusted by placing a small electromagnet over the shunt mechanism and dialing up the new pressure. When reprogramming the shunt, extreme care should be taken in precisely locating the active shunt mechanism by palpation, and carefully centering the electromagnetic programmer over it; otherwise the valve may program to a completely wrong setting. In cases where palpation is difficult, precise localization of the active shunt mechanism can be facilitated by a preliminary Xray with temporary placement of a radiopaque marker (beebie), which can then be removed prior to programming once the proper spot is identified. After programming the valve, one must confirm that the valve was correctly set by obtaining an Xray (see Figure 33-9); the setting can be difficult to see on Xray, and requires that the beam to pass first directly perpendicular to the shunt mechanism, then through the head, then to the Xray plate. A small dot on the right side of the device indicates proper orientation of film and placement of shunt (right hand rule); if it appears in the left, either the film was taken with the device against the Xray plate or the shunt is implanted upside down. There is a procedure for programming an upside down shunt, and the reader is advised to check with the

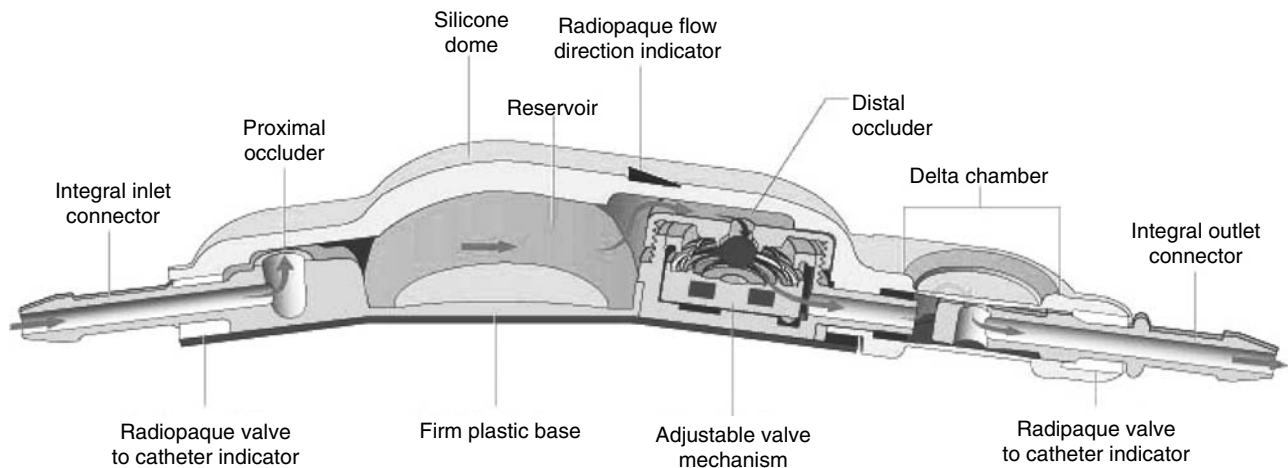


FIGURE 33-8

Medtronic PS Medical Strata (programmable) valve

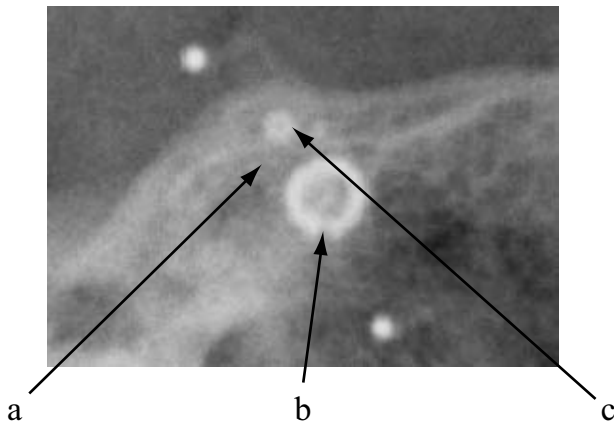


FIGURE 33-9

Xray of Codman Hakim Programmable Shunt mechanism.

- a. Points toward the location of the ruby ball and its seat.
- b. Points to the notch in the circle, which is the cam rotor determining shunt pressure setting. Shunt setting is determined by the location of this notch.
- c. This is the right hand marker indicating film is done correctly for reading.

*Note:* the small circles at the top and bottom are small bees used by examiner to help confirm location of active shunt mechanism.

manufacturer in this instance. The Xray appearance is then compared with the settings template to identify the setting.

Patients with programmable valves can have MRI scans, but must have an Xray to check valve setting and may need reprogramming afterwards; valve settings were changed by MRI in 26.8 % of patients (147). Valve settings may also be changed by any very large magnets in the environment, and even by “filliping” of the shunt (abrupt manual manipulation such as flicking it with a finger)(154).

Valve pressure settings can be lowered for inadequate response to shunting, or raised for symptoms of overdrainage. Shunt settings should never be raised more than 30 mm at one time. Orthostatic headaches from overdrainage are particularly responsive to reprogramming of the valve, with headaches improving in 71% of patients (148). In some patients who develop subdural hematoma after shunting, surgical drainage of the subdural can be avoided by turning up the opening pressure of the valve(148). In two recent series reprogramming was performed in 41- 64% of patients with programmable valves at least once, and some had multiple adjustments (147–151). Based on the assumption that an adjustment of 50 mm or more would have warranted surgically changing the valve if it were not programmable, a cost benefit analysis of 541 programmable valves indicated

that the increased cost of the programmable valve was outweighed by the cost savings in avoiding additional surgeries (149). The possible benefit of reprogramming shunt valves during rehabilitation has only just begun to be explored. In one study of 114 patients, adjustments were deemed necessary in 13% of patients, and changes of 20–70 mm in steps correlated with significant functional improvement as scored on the Barthel index (151).

The PS Medical Strata valve has five settings which can be adjusted at bedside with magnetic tools. It has a ruby ball in cone with circular spring design, and includes an antisiphon component of the type found in the delta valve. Although is less flexible with regards to valve pressure settings (only 5 instead of 18 settings), the adjustment tools are easy to use, and the shunt setting can be confirmed at the bedside, making confirmatory Xray optional. One interesting aspect is that the relative positions of the Strata’s delta chamber and the ventricular tip of the catheter can substantially effect the amount of anti-siphon effect of the Strata system (83, 122, 153).

*Gravitational Shunts* Overdrainage of shunts has been particularly problematic because of the negative intraventricular pressures generated in the upright position by the column of fluid in the distal shunt tubing and the related siphon effects. In order to address this problem in a specific manner, gravitational shunts are designed with a higher opening pressure in the upright position than supine. The one used most extensively has been the Miethke Dual Switch Valve (113, 155–157). This is actually two valves in one, ingeniously designed so that the lower pressure valve opens in the supine position but is mechanically closed off by a ball in the vertical position, forcing flow through the higher pressure half of the valve when upright. A related invention is the Shunt Assistant valve (157, 158), essentially a gravitational antisiphon device which can be put in series with another valve, such as the Codman Hakim programmable valve. In the vertical position a tantalum sphere compresses a sealing ball to substantially increase the orthostatic opening pressure of the valve system specifically. At least 185 patients with normal pressure hydrocephalus have been carefully diagnosed and treated with either Meithke Dual switch valves or a combination of the Codman Hakim Programmable valves combined with the Shunt Assistant valve. Good or excellent outcome was described in 70% of patients and the incidence of overdrainage was only 4% (157). Of great interest, the patients with greatest favorable clinical response to shunting had minimal or no significant change in ventricular size post shunting (156, 157). It has been suggested that part of the reason for favorable outcome in this patient group may have been the avoidance of complications of overdrainage so commonly



seen after implantation of more conventional shunt systems.

## VASCULAR COMPLICATIONS

### Traumatic Aneurysm

*Intracranial Traumatic Aneurysms* Traumatic intracranial aneurysms are rare; they comprise less than 1% of all intracranial aneurysms (159–161) and are more common after missile injuries than closed head injury. In missile injuries direct contact of missile or bone fragments with the artery is common, whereas in blunt injuries up to 40% of cases do not have associated fracture (161). Traumatic aneurysms can be classified as true, false, mixed, or dissecting types, but false aneurysms are the most common (162–164). In true aneurysms, the adventitial wall is preserved, whereas in false aneurysms all elements of the vascular wall are disrupted and blood is contained only by the surrounding arachnoid, hematoma, or brain parenchyma. Mixed aneurysms have a combination of true and false elements. In dissecting aneurysms, blood channels within the vessel wall, effectively narrowing or occluding the vessel itself.

Common clinical presentations of traumatic intracranial aneurysms include seizures, focal neurological deficits, altered consciousness, and severe persistent headache (159, 161). Traumatic intracranial aneurysms are highly unstable and prone to rupture (162, 163); in fact, although the time interval from injury to rupture varies from days to years, 90% bleed within 3 weeks of injury (160, 163). The most common locations for traumatic aneurysms are the distal middle cerebral branches, distal anterior cerebral artery, and proximal carotid and vertebral arteries (161). Traumatic petrous and cavernous carotid aneurysms are often associated with basilar skull fracture, while supraclinoid carotid aneurysms are sometimes associated with orbital or anterior clinoid process fractures (161). Epistaxis, pharyngeal mass, and delayed cranial nerve palsy have also been described with aneurysms near the skull base (161, 165), and traumatic aneurysms should be suspected in patients with delayed subarachnoid or intracerebral hemorrhage. Although angiography remains the definitive test for diagnosis, it is now recognized that the combination of Magnetic Resonance Angiography (MRA) with perfusion weighted Magnetic Resonance Imaging (MRI) can be a very useful screening tool, especially given the difficulty of clinically identifying patients with these aneurysms (161).

Treatment of traumatic intracranial aneurysms can be problematic since they are typically false aneurysms and therefore cannot be clipped (162–164). Because the parent vessel often must be sacrificed, extracranial to intracranial distal revascularization procedures are sometimes performed at the time of definitive treatment (161).

Recently developed endovascular approaches have often been useful, including detachable balloons, detachable coils to occlude the parent vessel, or stents to exclude the aneurysm from the circulation while maintaining the patency of the parent vessel (161).

*Cervical Arterial Trauma Including Dissection* Traumatic injury to the cervical internal carotid or vertebral arteries may be seen after penetrating injuries, or after hyperextension and flexion neck injuries, as in motor vehicle accidents; many patients with blunt injuries show little or no overt external neck trauma (161). The incidence of injury to the carotid artery in patients with TBI has been estimated at 0.5% (161). When carotid injury occurs, mortality is estimated at 20–40% and neurologic deficits are seen in 80% of survivors. Presentation is typically that of infarction in the distribution of the involved vessel, either secondary to thrombosis, embolism or dissection. For example, after carotid artery trauma hemiparesis and hemisensory loss occur, but onset of these symptoms exceeds 10 hours from initial injury in half of cases, and is sometimes delayed for up to 48 hours (161). Acute headache can be a very important clue to the early diagnosis of arterial dissection, occurring in 60% of cases of carotid dissection, and slightly less often with vertebral artery dissection, where the headache tends to be occipital (166). Other important clues to possible cervical carotid injury include mandibular fracture, neck pain, pulsatile tinnitus, visual changes, lower cranial nerve palsies, and ipsilateral Horner's syndrome (161). Revascularization or direct repair is sometimes attempted for carotid dissection, but only if it can be done within 4 hours of onset in a conscious patient (162). Otherwise management is medical, with consideration of antiplatelet or anticoagulation therapy depending on clinical course and associated injuries. Anticoagulation with heparin or coumadin has been the traditional management when not contraindicated, but lacks a strong evidence base (166).

### Carotid Cavernous Fistula

*Types and Presentation* Traumatic carotid cavernous fistulas are typically direct fistulas from the internal carotid artery. Classified as type A, with fast flow and high pressure, they contrast with spontaneous carotid cavernous fistulas (types B, C, and D), which have low pressure and slow flow and typically receive dural blood supply (167, 168). The cavernous sinus is anatomically unique in that a large artery passes through a large venous space; for this reason a tear in the arterial wall alone can create an arteriovenous fistula without any additional venous anomaly (169). Visual impairment is a major presenting symptom and concern for further visual loss is a frequent management concern in patients with carotid cavernous fistula. Additional presenting signs of carotid cavernous fistula

include supraorbital bruit, exophthalmus, orbital congestion, oculomotor palsies, and trigeminal nerve involvement (167, 170, 171). Pulsatile exophthalmus is seen in carotid cavernous fistula but also has been described in a patient with orbital encephalocele and hydrocephalus (172). Pulsatile tinnitus may result from arteriovenous fistulas and malformations or from altered jugular venous flow (173–177). Onset of carotid cavernous fistula is often delayed; 43.5% are diagnosed over 1 month after trauma (170). Angiography is the definitive diagnostic test.

**Treatment** Spontaneous closure of a carotid cavernous fistula has been described in some patients; it is much more likely with a spontaneous low-flow fistula than with the traumatic high-flow fistula. Patients have been trained in intermittent manual compression of the cervical carotid artery with the contralateral hand. Although the success rate is lower with direct fistulas, 17% of patients had successful closure with this technique (178). The definitive treatment of traumatic carotid cavernous fistula has become the endovascular placement of detachable balloons (168, 179, 180). Successful fistula closure was accomplished by the detachable balloon technique in 92 of 95 cases of traumatic carotid cavernous fistula, with preservation of the internal carotid artery in over 70% of cases (168).

## LATE INTRACRANIAL MASS LESIONS

### Subdural Hematoma and Hygroma

**Differences Between Acute and Chronic Subdural Hematoma** Subdural hematoma is the most common late-presenting mass lesion. Although acute, subacute (3–20 days), and chronic (3 weeks or more) subdural hematomas

are distinguished by time of detection after injury, it is important to recognize that chronic subdural hematoma is a different pathophysiologic process than acute subdural hematoma, not simply an older blood clot (181–185). As a result, differences are also seen in the epidemiology, clinical presentation, prognosis, and treatment techniques (73, 182, 184) (Table 33-3). The incidence of chronic subdural hematoma peaks in the seventh and eighth decades, and only 60–65% of patients have known TBI (184, 186) Male predominance (70–90%) and parietal location (91%) are characteristic (181, 184). Headaches are a cardinal symptom (184, 187), sometimes following a symptom-free interval. Three major clinical presentations include hemiparesis (40%), personality or intellectual change (30%), and signs of increased intracranial pressure, including papilledema (20%) (181). In contrast with acute subdural hematoma, seizures are relatively uncommon with chronic subdural hematoma (4–7%), and ongoing anticonvulsant prophylaxis is not routinely required (188), although some authorities have recommended it in the immediate postoperative period (187). Transient episodes of aphasia or sensorimotor disturbance have also been described with chronic subdural hematomas, mimicking either transient ischemic attacks or seizures, and resolving after the immediate postoperative period following surgical drainage (189, 190).

**Scan Findings in Subdural Hematoma** CT scans characteristically show decreased density in chronic subdural hematoma. However, the isodense appearance characteristic of subacute subdural hematoma may last longer than 1 month in some instances (191). In questionable cases, contrast enhancement helps to identify isodense subdural collections (192). In other cases, a layer of isodensity or increased density is seen below a hypodense layer; this sedimentation level likely reflects interval rebleeding (192, 193). Isodensity at the medial margin

**TABLE 33-3**  
*Differences Between Acute and Chronic Subdural Hematoma*

FEATURE	ACUTE SUBDURAL HEMATOMA	CHRONIC SUBDURAL HEMATOMA
Age Peak	30–49 years	60–70 years
Known TBI	Virtually all	60–65%
Clinical Presentation	Acute mental status change, focal signs, seizures, increased intracranial pressure	Personality or chronic mental status change, headache, hemiparesis, increased intracranial pressure
Composition	Blood clot	Fluid, membrane
Pathophysiology	Venous bleeding especially from torn bridging veins	Initial subdural hygroma or initial venous bleeding, inflammatory process with leaky macrocapillaries, disordered hemostatic mechanism
Treatment	Craniotomy	Burr holes, twist drill craniostomy, or craniotomy

of a fluid collection also may represent fresher bleeding (192). Compared with CT scan density, the factors determining signal intensity on MRI are much more complex. Whereas acute subdural hematoma shows increased CT density, subacute and chronic subdural hematoma have increased signal on MRI (29, 187, 194). Subacute subdural hematoma is seen as a hyperintense collection on T1-weighted images, largely because of the presence of methemoglobin. Chronic subdural hematoma presents with more variable signal intensity on T1-weighted images but consistently shows increased signal intensity on T2-weighted images (29, 187, 194). In addition, fluid collections that are homogeneous on CT sometimes show hypointense septations and mixed intensities on MRI. In some instances, a sedimentation level of a hyperintense (fluid) upper layer and hypointense (more cellular) lower layer is seen. Such findings are consistent with the conceptualization of subdural hematoma as an ongoing process with interval rebleeding rather than a static collection of blood. As described below, an outer membrane is characteristic in chronic subdural collections; this membrane enhances significantly with gadolinium on T1-weighted imaging in many cases (29). Although CT and MRI are the definitive tests for diagnosing subdural collections, abnormalities also are seen in the electroencephalogram (EEG) and in testing of cerebral blood flow. In addition to delta slowing on the side of a subdural collection, ipsilateral suppression of voltage is seen on EEG in 25% of patients (184, 186). Diffuse reductions in cerebral blood flow preoperatively often show a recovery 1 month postoperatively (195).

*Pathology of Chronic Subdural Hematoma* On pathologic examination, the fluid of chronic subdural hematoma shows a range of color and appearance, including brown-black, dark red, amber-brown, and almost clear and watery (184, 194). Coagulated masses of blood and fibrin are sometimes present. A thicker outer membrane attached to the dura and thinner inner membrane bordering on the arachnoid are characteristic (184). Enlarged ectatic capillaries, often called giant capillaries or sinusoids, are prominent on the outer membrane and associated with inflammatory cells, fibroblasts, and hemosiderin-laden macrophages (184). With age, the outer membrane also may become calcified.

*Subdural Hygroma* Subdural hygroma has been described as a subdural collection of cerebrospinal fluid, often with a modified composition (196). The distinction between subdural hygroma and chronic subdural hematoma has often been unclear in the literature, partly because subdural fluid composition varies, sometimes exhibiting xanthochromia or containing blood products. Also the term hygroma has sometimes been used to describe low density extraaxial collections on CT scan

without mass effect (196), even when identification of cortical veins lateral to the collection on MRI might more correctly identify it as subarachnoid fluid associated with atrophy (29). It has been proposed that a tear in the arachnoid may acutely allow CSF into the subdural space, and rare surgical documentation of this process has been provided (196). More often the development of subdural hygroma may be more gradual, and in these cases subdural hygroma formation requires separation of the dura-arachnoid interface and sufficient potential subdural space (143, 197–199). Low intracranial pressure (such as orthostatic negative pressures with a shunt), an underfilled CSF compartment, and atrophy are factors in creating sufficient subdural space (84, 118, 142, 143). Many patients have slight cranial asymmetry in the occipital region, with one side flatter than the other. In the supine position the cranium tends to turn slightly to the flattened side, and subdural hygromas tend to form frontally to the opposite side, or bilaterally in patients with a more symmetrical cranium (143, 197). The time course of hygroma development, enlargement, and in most instances resolution can be plotted.

*Pathophysiology of Chronic Subdural Hematoma* Recent work has significantly clarified our understanding of the relationship between subdural hygroma and chronic subdural hematoma, and the pathophysiology of their development. Chronic subdural hematomas occasionally develop from acute subdural hematomas, but more often chronic subdural hematomas develop from subdural hygromas (143). When hygromas do not resolve, a neomembrane forms from dural border cells, followed by leakage of blood from the fragile giant capillaries in the outer membrane induced by the inflammatory process (182, 200, 201). A disordered local hemostatic mechanism has been identified in fluid from chronic subdural hematoma (182, 183) with both excessive activation of the clotting system and the fibrinolytic system. Chronic subdural collections can sometimes show increasing density on CT scans for a period of weeks to months (143). The size of a chronic subdural collection may resolve spontaneously if absorption exceeds rebleeding, or alternatively the collection may continue to enlarge (143).

*Approach to Chronic Subdural Hygroma or Hematoma Management* Management of the patient with chronic subdural hygroma or chronic subdural hematoma is largely a matter of clinical judgement. Decreasing size of the collection, stability of the neurologic exam, and a lack of mass effect or compression on the underlying brain on CT or MRI scan are all factors which mitigate in favor of observation and serial scanning. While there is no set time interval for repeat scanning, in the absence of clinical worsening and depending somewhat on the size and appearance of the collection, a period of 2 to 4 weeks

can often be utilized. Alternatively, clinical worsening, the appearance of significant mass effect or midline shift on CT or MRI scan, or serial enlargement or substantial increase in CT density consistent with significant interval rebleeding would likely necessitate a surgical approach. It has often been the author's practice to obtain neurosurgical input early on, even when the immediate management is almost certainly conservative, so that a neurosurgical plan is in place and can be enacted quickly if circumstances warrant shifting to a more aggressive approach.

**Surgery for Chronic Subdural Hematoma** Surgical removal of a certain critical mass of fluid, containing degradation products from the subdural space may be important in interrupting the vicious cycle of disordered hemostasis and facilitating the recovery from chronic subdural hematoma (182, 183). Successful surgery, therefore, may reduce the residual volume to a degree that allows further resorption rather than fully removing the blood clot. Twist drill trephination or burr holes are the first line treatments for chronic subdural hematoma (181, 184, 202–204). Occasionally the presence of sizable clots or loculation may necessitate craniotomy, as is commonly done for acute subdural hematoma (182, 205). Postoperative drainage has been advocated to assist with brain reexpansion (182, 202). The hematoma cavity is commonly washed out with saline, and it has been suggested that continuous irrigation (to remove coagulation degradation products) may decrease the duration of drainage or frequency of recurrence (206, 207). Persisting subdural fluid was described postoperatively in 78% of patients, but had returned to normal by 40 days postoperatively in 27 of 32 cases, leading to the suggestion that reoperation should be avoided until at least 3 weeks postoperatively unless marked clinical deterioration occurs (208). Because of the active inflammation in the dural border cell layer and associated inflammatory cytokine production, postoperative anti-inflammatory medication/steroids have been suggested by some (182, 204). The overall prognosis from chronic subdural hematoma is much more favorable than the prognosis for acute subdural hematoma (184), although the residual deficits in the areas of personality and memory may be problematic (207). Patients with even severe neurologic deficits preoperatively may have successful outcomes (181), although the extent of preoperative deficit has been a useful predictor of outcome in some series (207).

### Epidural Hematoma

**Presentation** Although epidural hematoma is usually considered the most acute posttraumatic mass lesion, it presents more than 5 days after injury in 10% of cases (209) and may present as late as the second or third week after injury (210). Although epidural hematoma most

often presents in the temporal fossa (57–83% of cases) due to injury to the middle meningeal artery, delayed presentation is more common with extratemporal location, especially frontal or posterior fossa lesions (209, 211). Clouding or decreased level of consciousness is considered the most important sign of epidural hematoma (209). Onset is slowest with frontal lesions, and symptoms may be vague. Unilateral exophthalmus is an unusual sign that has been described with subfrontal epidural hematoma (211).

**Posterior Fossa Epidural Hematoma** Posterior fossa epidural hematomas are unique among epidural hematomas in that they are of venous rather than arterial origin. An occipital bone fracture is seen in 84.2% of cases and characteristically crosses the venous sinus, causing this venous bleeding (212). The venous origin helps explain why a slower clinical presentation may occur. A lucid interval is common, and progressive decrease in the level of consciousness is characteristic. Battle's sign is often seen, and neck stiffness, occipital headache, and vomiting may be prominent. Symptoms and signs of increased intracranial pressure as well as brainstem, cranial nerve, and cerebellar dysfunction are common (212, 213). Posterior fossa epidurals are not common; they are seen in only 0.3% of patients with TBI (212). However, they have the highest mortality rate (209) and are notoriously difficult to diagnose (211).

### Intracerebral Hemorrhage

Delayed traumatic intracerebral hemorrhage is defined as an intracerebral hematoma that is not visualized on initial CT but is seen on a follow-up study. It occurs in 5.6–7.4% of patients with severe TBI (214). Time of onset is typically about 24 hours after original injury (214), and 80% of cases occur within 48 hours of injury (187). Cardinal signs of delayed traumatic intracerebral hemorrhage include decreased level of consciousness, focal signs, or seizures (215). Factors postulated to play a role in the pathogenesis include dysregulation of blood flow, coagulation disorders, and removal of tamponade effect by evacuation of another mass lesion, such as an epidural or subdural hematoma. Outcome is worse with temporal lobe location, which shows an increased incidence of herniation (216).

## SUMMARY AND FUTURE DIRECTIONS

### Risks and Infections

**Risks** Conditions associated with increased risk of infection have been discussed including skull fractures and penetrating injuries, and cerebrospinal fluid (CSF) fistula. With the exception of penetrating wounds, where

antibiotic prophylaxis is almost universal, the approach to prophylaxis remains controversial. A large well controlled study would be helpful to resolve the indications for antibiotic prophylaxis. It appears that the ongoing presence of a fistulous connection between the atmosphere or sinuses and the intracranial compartment (through the skull and dura) implies a very substantial risk for development of meningitis, even in the absence of overt CSF drainage, and sometimes even years after injury. Therefore an aggressive approach to identification and closure of a CSF fistula is warranted. Glucose testing is not reliable in suspected CSF rhinorrhea, but assessment of beta-2 transferrin assay is reliable.

Cranioplasty was often delayed in the past partly because of concerns of complications including infection if performed early. However it has recently become clear that some patients with craniectomy exhibit the syndrome of the trephined with a markedly ingoing flap in the area of missing bone. These patients not only tolerate having cranioplasty performed earlier, but sometimes actually show significant neurologic improvement after cranioplasty is performed.

**Infections** Meningitis typically pursues a fulminant course. The exception is infection of a ventriculoperitoneal shunt, which tends to pursue a very indolent course without overt signs of acute infection. Shunt infection can only reliably be diagnosed by tapping the shunt, not by lumbar puncture, and *Staphylococcus epidermitis* is the most common organism and in this setting is usually real rather than a contaminant.

Subdural empyema and brain abscess are rare complications of TBI except with compound depressed skull fracture, CSF fistula or penetrating wounds. Subdural empyema typically presents with acute signs of infection, while brain abscess often presents as a mass lesion without evidence of acute infection. Lumbar puncture is contraindicated for both, while newer imaging modalities such as diffusion weighted MRI are proving useful in establishing the diagnosis in some cases.

### Hydrocephalus

**Diagnosis** Ventriculomegaly is common after severe TBI, but it remains difficult to distinguish dynamic hydrocephalus from ex-vacuo ventricular dilatation. Both the CSF tap test and lumbar infusion studies, possibly combined with SPECT studies, appear to have utility in sorting difficult cases. Further research on CSF drainage trials and lumbar infusion testing in TBI patients with possible hydrocephalus would be valuable, and might spur increased routine use of these studies.

**Shunts** The mechanisms, complications and innovations in shunt technology have been reviewed at length. Pro-

grammable shunts may offer significant promise specifically for the patient with post-traumatic hydrocephalus, given the frequency of communicating hydrocephalus without high pressure, difficulty in predicting appropriate pressure settings, and uncertain magnitude of clinical response. However further research demonstrating proven superiority over standard shunts in this population is still needed, especially as use of these shunts is complex and can be labor intensive on the part of the physicians managing them. Overdrainage has been a major complication with ventriculoperitoneal shunts, and the recent development of shunt systems which effectively drain at a higher opening pressure standing than supine could be a major advance.

### Late vascular and mass lesions

**Vascular Complications** Traumatic intracranial aneurysms are uncommon, but are often false aneurysms and extremely prone to rupture. Clinical features to aid diagnosis are discussed, and MRA and perfusion weighted MRI may be helpful for screening. Endovascular approaches including coils and stents have recently changed management considerably. Carotid cavernous fistula is the most common post-traumatic arteriovenous malformation, and often presents with visual symptoms along with localizing signs of cavernous sinus involvement. Endovascular approaches with balloons have proven effective. Trauma to the cervical carotid and vertebral arteries can induce thrombosis or dissection. Presentation with severe head and neck pain can be a diagnostic clue prior to development of cerebral infarction, and anticoagulation is often utilized.

**Late Mass Lesions** Subdural hygroma and chronic subdural hematoma are frequently encountered, whereas delayed epidural and intracerebral hematomas are less commonly seen. Posterior fossa epidural hematoma is of venous origin, typically in association with occipital fracture, and a rare but serious complication. Chronic subdural hematoma is a clinically distinct entity from acute subdural hematoma, both in terms of epidemiology and management. It now appears that many chronic subdural hematomas develop from a subdural hygroma. The approach to management of chronic subdural collections is discussed at length.

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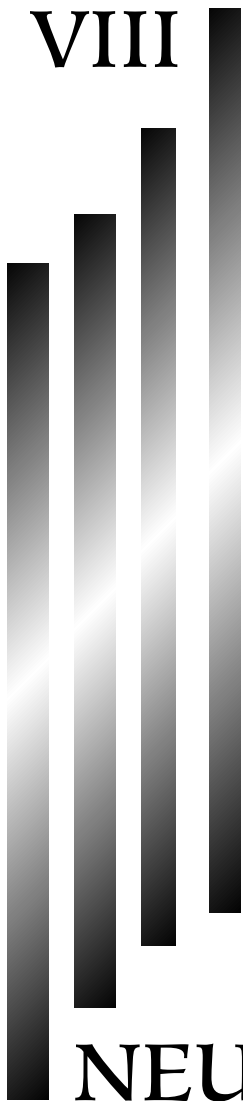


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VIII



NEUROMUSCULOSKELETAL  
PROBLEMS

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# 34

## Complications Associated with Immobility after TBI

*Kathleen R. Bell*

### INTRODUCTION

Immobilization of the human body has long been known to affect physiology in ways detrimental to normal function, even in the time of Hippocrates (1). Despite this knowledge, prolonged bedrest was used for many years in the treatment of medical disorders. However, studies emanating from the manned space program since the 1960's defining the effects of a gravity-free environment have clarified many of these effects in healthy humans. Most of the studies performed on animals, however, rely on hindlimb suspension models of immobilization and many studies on humans rely on the head down tilt position in bed to mimic microgravity. None of these conditions precisely reproduces the conditions of prolonged bedrest in a medical situation. Nonetheless, general principles regarding the effect of inactivity on the body can be derived from these experiments. As an additional complicating factor in severe traumatic brain injury (TBI), the effects of immobilization may be prolonged and worsened by a number of disorders stemming from the brain injury itself such as posturing, spasticity, dysautonomia, endocrine abnormalities, and other body system injuries. Thus the importance of prevention and prompt management of these disorders is highlighted in addition to early mobilization of the patient with TBI.

Prolonged bedrest brings about reduced function in multiple body systems simultaneously. For example,

deconditioning is a diagnosis in its own right (2). Deconditioning results from reduced functional capacity of both the musculoskeletal and cardiovascular systems; changes to one system are unlikely to be significant without accompanying decrements in the other system. The effects of deconditioning can be studied in young, healthy experimental subjects, eliminating the effects of pathology. The effects of mobilization and exercise on this group emphasizes the importance of early mobilization for those with illness or injury (2).

This chapter seeks to address those general aspects of immobility that may be seen in any situation where prolonged bedrest occurs and to discuss the impact of traumatic brain injury on related causal factors and treatment (Table 34-1). There are very few studies that actually examine the specific effects of immobility on persons recovering from TBI (or any other illness or injury) so associations and recommendations are made derived from literature on healthy individuals or those with other disorders.

### EFFECTS OF IMMOBILITY ON THE PERSON WITH TRAUMATIC BRAIN INJURY

#### Musculoskeletal System

Significant changes occur in the musculoskeletal system in the first 4–6 weeks of immobilization affecting all

**TABLE 34-1**  
***A Summary of the Effects of Immobility on Organ Systems with Associated TBI-Related Physiological Stressors***

ORGAN SYSTEMS	POSSIBLE EFFECTS	TBI RELATED DISORDERS
Musculoskeletal	Muscle weakness, osteopenia, muscle and joint contracture	Spasticity and other movement related disorders, paresis, associated trauma
Respiratory	Hypoventilation, pooling of secretions	Tracheostomy, altered immune function
Cardiovascular/Hematologic	Deconditioning, postural hypotension, thromboembolic disorders	Autonomic instability, hyperhidrosis, paresis, fluid and metabolic disorders
Dermatological	Pressure ulcers	Paresis, catabolism, dysphagia
Neurological/Psychological	Sensory deprivation, balance disorder	Special senses disturbances, cognitive impairment, vertigo
Metabolic/Neuroendocrine	Volume contraction, hypercalcemia	Sodium disorders, hyperhidrosis, paresis
Gastrointestinal and Urologic	Constipation, reflux, and urinary stasis	Dysphagia and impaired cognition requiring enteral feeding

components of the system, including up to 40% loss of muscle strength, decrements in bone density, and shortening of collagen-containing tissues. These changes are the results of a lack of the usual weight-bearing forces acting in the vertical position and the decrease in muscular contraction especially in the postural muscles (3). While these types of changes occur in even healthy young people, the effects are magnified in populations such as the elderly with baseline alterations in muscle strength and bone density. One concern is whether persons subjected to prolonged periods of bedrest will be at higher risk of osteoporosis as they age if stores are not recovered (3). As we will see, persons with TBI are likely to be more profoundly affected as well, because of associated conditions.

**Bone Density Loss** Bone is constantly undergoing alteration and remodeling during normal activities. The activity of osteoclasts that reabsorb mineralized bone matrix and osteoblasts which are responsible for the synthesis and mineralization of bone is governed by mechanical stresses and systemic stimuli. Participants in the regulation of bone density include mechanical stresses, hormones, growth factors, and cytokines. In addition to osteoclasts and osteoblasts, chondrogenitor cells may become either chondrocytes covering the joint surface of bone or growth plate chondrocytes that are the basis for metaphyseal bone formation. These cells form bone modeling units (BMUs) whose activity is altered by physical activity or immobility, nutrition, aging, and illness (4). Specifically, skeletal muscle activity at least partially regulates bone density maintenance via growth factors (e.g., IGF-1) even during periods of disuse (5).

Chronic illness or prolonged recovery from trauma such as that seen in TBI is most likely associated with the

growth hormone/IGF-1 axis, along with impaired thyroid and gonadal function (4, 6). Immobilization specifically is associated with a moderate decrease in bone resorption but an even larger decrease in mineralization of bone matrix (7, 8). A negative calcium balance occurs within a week of bedrest, and 20 weeks of bedrest in healthy, young men results in a 60% increase in urinary calcium. Fecal calcium loss also occurs in conjunction with reduced intestinal absorption (3). There is decreased bone mineral density in the lumbar spine, femoral neck, tibia, and calcaneus but not the radius noted in young men on 4 months of bedrest (9). There are no significant changes in serum parathyroid hormone or in serum 1,25-dihydroxyvitamin D during bedrest in healthy men, but persons with spinal cord injury have been shown to have decreased levels of both (10). In persons with TBI, an additional factor to consider in factoring the degree of bone loss is the frequent presence of hemiplegia or other patterns of paralysis. Data from persons recovering from stroke and other neurologic disorders offer some insight although not directly applicable to the brain-injured population because of the differences in average age and degree of paralysis and immobility. Bone loss early after stroke appears to be primarily due to increased bone resorption while later bone loss is more clearly related to the degree of paresis and vitamin D levels (11). 1, 25-dihydroxyvitamin D production appears to be inhibited (12). Nearly all fractures after falls occur on the hemiparetic side in stroke patients (13). Bone mineral density was significantly lower in both femurs in stroke patient who were non-ambulatory after stroke. The difference in bone loss only on the hemiparetic side between the non-ambulatory and ambulatory patients was also significant. Most of the loss occurred within the first seven months

after stroke (14). Bone density loss in the limbs is even more striking after spinal cord injury; however, vertebral bone density is not significantly compromised because of continued weight-bearing in the seated position (15).

Recovery of bone mineral density after loss is quite slow for longer periods of immobilization. Although dogs recover to baseline in 12 weeks after 12 weeks of immobilization, for longer periods of immobility, bone did not recover even after 7 months (16). Calcaneal bone density deficits have been noted in astronauts even 5 years after space flight (3, 17). There are few studies of reversing or minimizing bone loss after neurologic insults. Vitamin D and calcium supplementation have been demonstrated to be helpful in preventing fracture in elderly patients but caution should be used after stroke in the presence of hypercalcemia (18, 19). Etidronate which inhibits bone resorption has been studied in spinal cord injury and stroke and may be effective in preventing bone resorption (20, 21). Clenbuterol, a beta-2-agonist, has been tested to prevent muscle and bone loss in rats with a significant prevention of muscle atrophy and accompanying lessening of bone mass loss (22).

*Muscle Weakness and Atrophy* There is no doubt that muscle strength and size are affected after prolonged bedrest. As might be predicted, the weight-bearing muscles of the lower limb are affected to a greater degree than the muscles of the arm (23). There are even more local differences in the degree of muscle atrophy. The knee extensors lose more mass than do the knee flexors (24). There are a number of possible mechanisms that result in muscle weakness and atrophy that are further discussed below.

*Protein Breakdown* By the fifth day of bedrest, there is a significant increase in the urinary excretion of nitrogen, peaking in the second week of bedrest. This reflects protein degradation and is an early marker of muscle atrophy (25–27). The cross sectional area of muscles is reduced 7–14% in 4–6 weeks of immobilization, especially in muscles responsible for resisting gravity such as the knee extensors (28, 29). Lower limb muscles are affected more than upper limb muscles.

*Decreased Protein Synthesis* Shortly after a limb is immobilized, decreases in total RNA and protein synthesis can be seen in muscles (30). Some alterations in pre-translational and translational mechanisms for protein production begin within six hours of immobilization, reflected in decreased alpha-actin and cytochrome c protein synthesis and decreased cytochrome c mRNA in rats (31–33).

Regrowth after inactivity-induced atrophy involves a number of mechanisms including 1) increased protein synthesis, 2) continued elevations of protein degradation,

3) increased proliferation of muscle precursor cells, 4) and increases in myonuclear number (myonuclei per 100 myofibers) (30). Unfortunately, muscle regrowth after atrophy is not always complete, especially in the elderly (34, 35). As a clinical example, muscle wasting in 64-year-old patients after total hip arthroplasty persisted 5 months postoperatively (36). This limited regrowth may be due to low satellite cell numbers and lower levels of growth factors (such as IGF-1) (30).

*Disruption of Antioxidants in Skeletal Muscle* In pathological conditions, such as post-trauma catabolism, other mechanisms may be at play in the volume of muscle loss during bedrest and immobilization. Typically, antioxidant protein and scavenger protection protect skeletal muscle against oxidative stress. However, during hindlimb unloading in rats, there has been demonstrated large shifts in superoxide dismutase activity with impaired antioxidant activity (decreased catalase, glutathione peroxidase, and nonenzymatic antioxidant scavenging capacity) (37–39). This disruption of protection can result in muscle fiber damage and loss that, when combined with a state of protein loss after severe trauma, is accelerated.

There is disagreement between animal and human experiments on which muscle fibers appear to be most affected by this loss of volume induced by immobilization. Generally, in animals, slow-twitch fibers are predominantly affected. In humans, however, fast-twitch fibers appear to be most affected. It is possible that this may be somewhat misleading as the relative sizes of slow- and fast-twitch muscle are different in rats and humans (3).

There is some evidence that some of this muscle atrophy and loss of oxidative capacity can be prevented by isometric exercise during the period of immobilization (40, 41). Isometric exercises appear to be more effective in slow tonic muscles like the soleus as compared to the fast-twitch muscles such as the gastrocnemius (40). In addition to having a salutary effect on bone density, clenbuterol also appears to reduce muscle degeneration in dystrophic or denervated muscle (42). In addition, there is some evidence that oral creatine supplementation enhances the muscle hypertrophy response to exercise after a period of immobilization (43).

Not unexpectedly, these findings suggesting protein breakdown and a loss of muscle mass would lead one to predict an accompanying decrease in muscle strength. Microgravity studies have demonstrated that 30 days of bed rest will result in an 18–20% decrease in knee extensor strength (44, 45).

Endurance is also decreased after prolonged immobility. Decrements up to 17% are noted in torque production in limbs unloaded for 4 weeks; this does not recover to baseline even after 7 weeks of recovery (46). These findings may be due to changes in muscle oxidative



enzymes as well as decreased oxygen delivery to muscle after disuse (3).

Part of the loss of muscle strength observed after prolonged bed rest is the result of decreased efficiency in motor neuron recruitment. While electromyographic activity is reduced by half in muscles that are shortened, there does not appear to be a relationship between the electrical activation of muscle and the relative decrease in muscle mass (47). However, there is evidence for reduced motor neuron activation after immobilization and a subsequent need for increased neuronal activation to produce the same degree of muscle force output (48–50). These neuromuscular inefficiencies can be totally reversed with training after the cessation of bedrest (49). This type of data also supports the notion of early movement and weight-bearing, as much of the muscle loss seen in the first 2 weeks of bedrest can be easily restored.

*Joint Contractures* There are a number of changes in connective tissue and muscle during immobilization of a limb that can result in a loss of passive range of motion in a joint. For instance, studies have demonstrated reductions in both the length and diameter of muscle fibers and in muscle extensibility (51–53). Additionally, there is an increase in intramuscular connective tissue and reduced capillary density in muscle (54, 55). In addition to these muscle changes, there is a significant increase in endomysial and perimysial connective tissue. More fibers are deposited perpendicularly to the adjacent muscle fibers. The network of collagen fibers become indistinguishable from each other (56).

Patients with TBI have an assortment of risk factors associated with their injuries that may contribute to the formation of joint contractures. Spasticity and rigidity may be extremely difficult to control in the acute stages of TBI. In examining the patient with TBI for contractures, it is important to assess the contribution of dynamic (spasticity dependent) aspects of joint movement limitation. It may be useful to perform a peripheral nerve block for this purpose. In later stages of TBI, postural control, especially of the axial skeleton, may lead to contractures of the neck and spine that are challenging to address. Weakness and prolonged maintenance of any posture will also contribute to joint contracture. Other general risk factors include age, edema, and diabetes mellitus. Reported incidence of ankle plantar flexion contractures in persons with acute moderate to severe TBI has ranged from 16–76%, depending on the definition of contracture (57, 58).

Prevention of joint contracture depends on the maintenance of proper joint position with the use of splints, adequate treatment of spasticity, and active and passive range of motion exercises to the joint several times daily. Standing is the optimal method of maintaining ankle range of motion and prone lying is very helpful to prevent hip flexion contractures. Serial casting is one option to

treat mild to moderate equinovarus deformities of the ankle and contractures of the upper limb (59, 60). Short changing intervals of 1–4 days were more effective than intervals of 5–7 days in restoring range of motion (60).

### *Respiratory System*

Many patients with severe TBI have tracheostomies for assisted ventilation and respiratory toilet in the acute stages. In addition, impaired alertness will result in a decreased drive for deep inspiration. Therefore, TBI patients are already at risk for pulmonary complications during their rehabilitation. Prolonged bedrest adds to that risk. Simulated weightlessness with a head-down tilt in healthy individuals demonstrates that the functional residual capacity of the lungs falls by 33% during this period with insignificant changes in lung tissue volume. Diffusing capacity decreases gradually to 4–5% below baseline values. Pulmonary blood flow also decreases by 16% (61). All of these changes result in higher risk for atelectasis and pulmonary infection. Treatment consists of early mobilization of the patient and aggressive pulmonary toilet with suction and the use of equipment such as the in-exsufflator to assist in the management of secretions.

### *Cardiovascular System*

Research on cardiovascular effects of immobility is drawn both from microgravity experiments during space flight and from experiments utilizing a head-down tilt position to mimic weightlessness. Obviously, these studies seek to maximize the effects of bedrest. Normal head-up positioning of patients in bed after TBI will mitigate the severity of cardiovascular effects.

*Reduction of Cardiopulmonary Functional Capacity and Postural Hypotension* Functional efficiency of the heart depends on both intravascular volume (hydrostatic forces) and coordinated filling and emptying of the ventricles (hydrodynamic forces). Normally, arterial pressures and certain levels of intravascular volume interact to maintain adequate body and cerebral perfusion in the face of gravity. However, when the body is placed horizontally for a prolonged period of time, about a liter of fluid is relocated from the legs to the chest area. Initially, this increases diastolic filling and increases the stroke volume of each cardiac contraction (i.e., the Frank-Starling mechanism). However, baroreceptor responses eventually result in a diuresis and loss of plasma volume within 24–48 hours (62). When a normal upright position is resumed, there is a sudden decrease in both ventricular filling and stroke volume that results in orthostatic symptoms (63). Cardiovascular baroreflex responses become attenuated without the challenges of baroreceptor unloading that comes from upright standing (64). Other factors

may include disordered sympathetic activation in combination with hypovolemia and diminished baroreceptor reflexes (65). Particularly interesting in the context of TBI is the involvement of brain autonomic nuclei such as the paraventricular nucleus of the hypothalamus that includes basal and reflex control of the sympathetic nervous system vasopressin and oxytocin release and secretion of corticotrophin releasing factor (66).

Other changes in cardiac function have been noted. After immobilization, the maximal oxygen uptake ( $\dot{V}O_{2\max}$ ) is reduced and the heart rate is increased in response to submaximal exercise (67). This equates to a loss in aerobic capacity of 0.9% per day over thirty days of bedrest (2). The heart rate during prolonged bedrest is higher for the same oxygen requirement (68). Part of this is related to the fluid changes noted above; these effects are much less during supine submaximal exercise (67). The heart rate is probably increased due to increased beta-adrenergic receptor sensitivity (68).

Simple replacement of volume does not abolish the orthostatic response (69). It appears that there are some alterations to the ventricles themselves during a period of prolonged bedrest leaving them less distensible (70). This appears to be an effect on cardiac muscle similar to the loss of muscle volume seen in skeletal muscle during prolonged immobilization (63). Actual muscle contractile properties seem to be preserved (71). The effects on stroke volume and cardiac output after prolonged bedrest will persist for at least a month (71). These effects are partially masked by an increase in peripheral volume and retention of sodium and, at least initially, an increase in sympathetic nerve activity (72).

Other peripheral mechanisms also come into play during prolonged bedrest. Deconditioning causes a reduction in red blood cell mass by 5–25% that may compromise blood oxygen-carrying capacity. However, the hematocrit generally remains stable during bedrest. Therefore, the effect of reduced blood cell mass is still unclear (68). As noted elsewhere in this chapter, there is a significant decrease in resting blood flow to the leg muscles and a reduction in capillarization. This is correlated with fatigability in calf muscles (73, 74) (See Figure 34-1 (68)). Interestingly, the role of the nervous system as another contributor to orthostatic intolerance has been recently promulgated. A subset of neurons in the paraventricular nucleus may be part of the puzzle in determining sympathetic nervous system excitation in response to blood volume and baroreflexes (66).

Reversing these effects requires not only the upright position and adequate fluid volume but also exercise that induces arterial baroreceptor loading (64). In animals, daily standing for only 1 hour per day prevented depression of myocardial contractility (75).

**Thrombogenesis** Thromboembolic disease is a well described risk in the setting of immobilization. In the

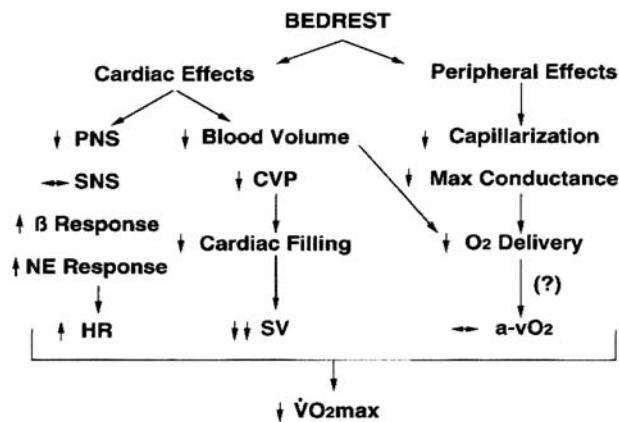


FIGURE 34-1

Model of cardiovascular mechanisms controlling maximal oxygen uptake during bed rest. (Permission requested: Convertino VA. Cardiovascular consequences of bed rest: effect on maximal oxygen uptake. *Med Sci Sports Exerc* 1997;29(2): 191–196.)

brain injured patient, this risk remains present with significant complicating factors for diagnosis and treatment. Often after significant trauma, each of the factors of Virchow's triad (stasis, endothelial damage and hypercoagulable state) is present on admission to the emergency room. In the TBI patient, one sequela of the injury may be hemiparesis which contributes to stasis in a more discrete and prolonged manner. Patients with TBI may also present with bleeding in the subdural or subarachnoid space, limiting the choice of treatment modalities. The TBI patient may also be impulsive and have considerable fall risk which may limit pharmacologic prophylaxis and treatment options. Identification and treatment of venous thromboembolism is therefore of increased complexity but of great necessity in the traumatic brain injured population (76).

Initial traumatic injury inherently carries with it risk for hypercoagulability when multiple organ systems are involved and bleeding is present at one or more sites. When bleeding occurs, the body initiates the coagulation cascade, a response that may be prolonged when blood remains present acting as a nidus for continued production of coagulation factors. In traumatic brain injury, bleeding may occur at any site in the body due to concomitant trauma, but is of particular concern in the subarachnoid or subdural space. The patient may require prolonged monitoring to ensure resorption or neurosurgical intervention to reduce mass effect due to bleeding, contributing to further stasis. A functional limitation of TBI may be hemiparesis or bilateral weakness which may persist following the acute period of immobility after trauma. Thrombi are noted to occur most frequently in the paralyzed limb of hemiparetic patients and more likely to occur in the proximal segment of the limb placing them at higher risk for

propagation (77). In a similar setting, DVT risk has been found to be comparable following brain tumor surgery as in the orthopaedic hip replacement population (78). The traumatic brain injury patient is also likely to have suffered endothelial damage with the initial inciting injury.

Identification of thromboembolism may be suspected clinically by the presence of a warm, edematous and painful limb. Unfortunately, the affected limb often exhibits no signs at all of thrombophlebitis therefore physical exam is unreliable for venous thrombosis diagnosis (79). The venous duplex exam is the mainstay of diagnosis. Testing carries high accuracy, is non-invasive and often readily available at the bedside (80). If pulmonary embolism (PE) is suspected by clinic findings of decreased oxygen saturation, tachypnea and pleuritic chest pain, studies to assist in diagnosis for PE should be employed as well as the above mentioned venous duplex to identify the potential source of the embolus. The D-dimer assay, spiral computerized tomography (CT) and ventilation-perfusion studies are all well accepted means to assist in diagnosis of pulmonary embolism. In the TBI patient, there are noted limitations to the use of these means of diagnosis. Following trauma, it is anticipated that D-dimer levels will be unspecifically high and therefore are not as helpful in diagnosis. Using D-dimer levels has not been shown to be useful in predicting deep venous thrombosis after acute TBI (81). However, a low D-dimer level may assist to rule out a pulmonary embolism if this be the goal. A ventilation-perfusion scan may be limited by any other concomitant pulmonary conditions such as pneumonia, secretions or atelectasis. The spiral CT is the most readily available tool for reliable diagnosis, albeit at a higher initial cost.

Treatment for identified thromboembolism is primarily pharmacologic by using unfractionated or regular heparin. Heparin acts initially by enhancing antithrombin III activity. In high doses, heparin also acts to inhibit prothrombin and platelet aggregation. This constitutes its efficacy in meeting the key treatment goals for PE and thromboembolism by inducing a hypocoagulable state and decreased potential for clot propagation (79). However, the TBI patient may have co-morbidities limiting the use of anticoagulation in their pharmacologic regimen. In the setting of TBI, the patient may have suffered a subarachnoid or subdural hemorrhage making anticoagulation undesirable. Further, impulsivity and significant fall risk may instill hesitation for use of anticoagulation in this population. In this setting, the use of retrievable inferior vena cava filters is increasing as a means to disrupt the clot pathway to decrease risk of pulmonary embolism. These filters are generally used in patients in whom recurrent PE has occurred despite treatment with anticoagulants or those in whom anticoagulant therapy is contraindicated (82). A review of multiple case series has indicated that these filters are successfully removed in 91% of cases; 9% of filters could not

be removed because of large trapped thrombus (83). It is important to note that these filters are associated with a 2-fold increase in the incidence of recurrent deep venous thrombosis. If it is safe to anticoagulate a patient, they should remain on therapeutic anticoagulation even with a filter in place for the recommended length of time (84).

Prophylaxis of thromboembolism to decrease the risk of a potential pulmonary embolism is the single most effective means of decreasing morbidity and mortality from venous embolic disease. Often patients are placed on mechanical and pharmacologic means of prophylaxis. The mainstays of mechanical means, compression stockings and sequential compression devices, may be appropriate in the TBI patient when in bed; however their use may be limited as they may interfere with ambulation and the rehabilitation process. The TBI patient may be appropriate for heparin or unfractionated heparin therapy if no contraindications exist. However, in the setting of intracranial hemorrhage, inferior vena cava filters may assist in limiting pulmonary embolism if initiated as a means of prophylaxis acutely after injury.

### *Integumentary System*

Pressure ulcers are a well-known complication of bedrest, particularly when complicated by paresis of any kind. Pressure ulcers are associated with increased mortality, morbidity, length of stay, and cost of treatment (85, 86). While TBI patients have not been specifically examined, immobility and decreased body weight are both independent risk factors for the development of pressure sores (87). After acute TBI, inadequate tissue perfusion because of unrelieved pressure at bony prominences is chiefly responsible for the development of pressure ulcers (88, 89). Pressure wounds heal best when kept moist with occlusive dressings. Other methods used to improve healing have included serial casting in patients with spasticity; the casts are thought to reduce friction associated with repetitive movements.

### **Neurological Systems**

*Effects of Bedrest on Cognitive and Psychiatric Function*  
Confinement to bed has been associated with a number of undesirable psychological and cognitive effects. Much of the data has come from studies on healthy young men as part of the space program research projects. These studies have used a 6-degree head-down tilt that more closely reproduces microgravity conditions than normal bedrest. Nonetheless, these studies have some application to medically-driven bedrest. These studies have noted enhanced levels of depression and emotional distress. In addition, impairments in overall cognitive capabilities have been described as well with self-reported confusion and depressed scores on cognitive testing (90, 91).

An additional area that may be affected by prolonged immobilization in bed is sleep. Chronic insomnia can be perpetuated by increased time spent in bed (92). Studies on elderly hospitalized patients on bedrest in poorly lit rooms have demonstrated that patients report poor sleep quality and that phase shifts for sleep are noted (93). Although these conditions have not been evaluated in patients with brain injury, it is reasonable to assume that worsening of confusion and sleep disorder can result from prolonged bed rest.

**Balance Disorder and Incoordination** Neuromuscular changes associated with inefficient recruitment of motor neurons may be partly responsible for the findings of increased postural sway, gait changes, and impaired kinesthetic sense after prolonged space travel (3, 94, 95). These changes in response to immobilization and bedrest may occur at multiple levels of the nervous system (96). For instance, it has been demonstrated that training can enlarge the size of the cortical area involved in the task. Conversely, it appears that there are reduced cortical responses after immobilization of a joint that are proportional to the length of time of immobilization. The amplitude of motor evoked potentials decreases after joint splinting during motor imagery tasks but not motor activation tasks (97). Other changes have been noted in the motor strategies used to perform a static muscle contraction after immobilization; some people were noted to produce a bursting pattern with reduced EMG amplitude in contrast to the pre-immobilization pattern of progressive increase in the amplitude of EMG activity (98, 99). The organization of neurons to provide maximal voluntary contraction appears to be diminished after 6 weeks of immobilization of a limb; peak force produced voluntarily during a maximum contraction was lower than that produced by electrical stimulation (100). Although the specific effects of immobilization on sensory inputs on control of movement have not been studied, there is evidence that sensory feedback such as vibration can evoke a cross-training effect and increase the power production capability of muscles (49,101).

### **Endocrine and Metabolic System**

There is no literature that directly addresses the influence of bedrest on the endocrine system or metabolism after TBI. A few points, however, may be interesting to review with an emphasis on how these factors may be affected by conditions after TBI such as hyperhydrosis (resulting in volume loss) and intrinsic damage to the pituitary-adrenal axis. Growth hormone resistance has been observed in chronic illness and/or malnutrition resulting from resistance at the hepatic growth hormone receptor leading to impaired hepatic IGF-1 generation and decreased growth hormone bioactivity. Growth hormone and thyroid hormone have synergistic actions and potentiate the effects

of each other on normal skeletal growth while acting on osteoblasts to stimulate bone remodeling. Involvement of growth hormone/IGF-1 and thyroid hormones can result in decreased skeletal growth, low bone mass, and low serum concentration of osteocalcin (4). Prolonged immobilization can be seen as a physiological stress and, as such, has been associated with elevated corticosterone levels and decreased plasma ACTH levels (102).

Hypercalcemia has been noted to be a particular problem in young adolescents who are immobilized for prolonged periods of time, particularly after spinal cord injury. However, there has been noted suppression of the parathyroid—1,25-dihydroxyvitamin D axis resulting in calcium loss as well as increased serum phosphorus and an elevated phosphorus renal threshold (103). Additionally, losses of magnesium in both feces and urine during immobilization in rats have been observed, resulting in a negative magnesium balance despite replacement (104). Nitrogen loss has been studied for many years; urinary nitrogen excretion peaks in the second week of bedrest at 20–43% above baseline (25).

Volume-regulating systems are affected by head-down bedrest (HDBR) and likely, by extension but to a lesser degree, to bedrest. Sodium and chloride are excreted as volume is lost, reflected by weight loss. Potassium excretion is delayed but then is elevated for the duration of HDBR experiments. An elevation in plasma renin activity accompanied these changes as well as a decrease in autonomic responses, with a shift towards sympathetic control (105). A high sodium diet does not seem to stabilize this loss of plasma volume (106).

### **Gastrointestinal and Urologic Systems**

**Constipation and Abnormal Absorption.** Intestinal absorption in general is decreased during the period of bedrest (3). More specifically, calcium absorption decreases from 31% to 24% of dietary intake over 17 weeks of bedrest (107). However, bone resorption accounts for a large proportion of the hypercalciuria seen after prolonged bedrest.

**Gastroesophageal Reflux** After severe traumatic brain injury, there are many issues that interfere with normal ingestion and digestion of food. Both neurologically based and cognitively based dysphagia predispose the patient to aspiration and almost always result in the use of parenteral feeding via a gastric or jejunal feeding tube. There has been little study of gastroesophageal reflux in patients on bedrest and none on patients with TBI or stroke, but it seems likely that the combination of dysphagia, tube feeding and related gastroparesis, and bedrest would increase the risk. One study of all patients admitted to a hospital via the emergency department found that, while symptoms of reflux were reduced in the whole population, those on bedrest or who received non-steroidal

anti-inflammatory drugs had increased risk of reflux-like symptoms (108). Patients with prolonged nasogastric tube feeding have demonstrated increased rates of esophageal damage (108).

**Urinary stasis** The recumbent position is associated with a reduced urinary flow rate and, although the difference in post-void residuals does not reach the level of significance, there is a trend toward higher volumes in recumbent voiding (109).

## PREVENTION OF COMPLICATIONS

In general, it can be said that any mobilization is beneficial in ameliorating the effects of prolonged bedrest. From the limited work done on the effects of exercise during prolonged bedrest, it is apparent that both isotonic and isokinetic exercises help to maintain cardiac functional capacity (peak  $\dot{V}O_2$ ), and help to preserve the red cell volume and positive body water balance. However, these two types of exercise had varying effects on quality of sleep and mental concentration (isotonic exercise surprisingly seemed to impair both) and had no effect on orthostatic tolerance when the experimental subjects were remobilized (110).

Remobilization after prolonged bedrest of the elderly patient with TBI should be done cautiously because the effects on bone density will be magnified in this population. Exercise directed at the weight-bearing trunk and lower limbs should be approached in a graduated basis.

Adequate hydration and nutrition are extremely important in maintaining bone, skin, and muscle integrity during rehabilitation after TBI, especially while the patient is on bedrest. Hydration is often difficult to maintain in patients with spasticity, dysautonomia, and hyperhydrosis. Range of motion and good positioning of the limbs, trunk and head are essential in preventing contractures and preserving the ability of the patient to utilize neurological recovery effectively at a later date.

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# 35

## Assessing and Treating Muscle Overactivity in the Upper Motoneuron Syndrome

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### INTRODUCTION

A lesion of the corticospinal tract produces an *upper motoneuron* syndrome (UMNS) (1, 2). Since the 19th century days of Hughlings Jackson, clinicians have classified UMN phenomena as positive or negative signs. Negative signs signified loss of voluntary motor behaviors (e.g. force production or dexterity of movement) that reflected *phenomena of underactivity or absence*. In contrast, positive signs such as increased stretch reflexes, spasms or co-contraction signified *muscle overactivity or phenomena of presence*, whether entirely new or merely enhanced beyond their normal presence. “Spasticity” was often used as a collective term for positive signs but, strictly speaking, spasticity is only one of many positive signs seen in UMNS (3).

In this chapter, we use “muscle overactivity” as a collective term for positive signs in UMNS because it captures the dynamic quality of excessive muscle contraction that is characteristic of the positive signs of the UMNS. The issue is not semantics. The pathophysiology of positive signs varies and so will their treatment. For example, co-contraction, likely of supraspinal origin, will differ in its treatment from clonus, a phenomenon of the segmental stretch reflex loop.

Studies have suggested that UMN muscles stiffen and develop contracture after being subjected to prolonged overactivity (4–6). Some have argued that such

viscoelastic and plastic changes, termed *rheologic* changes, can be more dysfunctional for the patient than many of the classic positive and negative signs (7). We agree with this perspective because we view the ubiquitous presence of stiffness and contracture, commonly responsible for disability in UMNS, as a third sign of UMNS. Negative signs represent the broad issue of impaired voluntary control and, when control is absent, muscle overactivity creates unbalanced forces across joints that restrain range of motion and promote stiffness and contracture. In our view, clinical problems seen in UMNS result from a combination of impaired production and control of movement (‘negative signs’), various forms of muscle overactivity (‘positive signs’) and a third sign of muscle stiffness and contracture (rheologic change). Moreover Herman has shown that muscle overactivity can be influenced by the stiffness characteristics of muscle. He studied 220 hemiplegic patients, divided into four clinical groups based on stretch reflex activity and physical extensibility of the calf muscles (4). Groups varied from an early hypotonic stage (group I) to a late “burned out” stage (group IV) that was characterized by increased tissue stiffness, lost range of motion and fixed contracture. For Group IV, Herman found reduced tissue extensibility to be linked with reduced tonic stretch reflexes. Increased resistance to passive stretch was due to changes in the physical stiffness of the triceps surae muscle. Patients with calf muscle contracture typically



walk with difficulty. From a therapeutic perspective, treatment of contracture is very different from treatment of negative signs of muscle underactivity and positive signs of muscle overactivity.

### POSITIVE SIGNS: 1. SPASTICITY

Spasticity is a term linked to stretch reflexes (8). It has a specific definition with respect to stretch reflexes but it has often been used confusingly as a collective term for all positive signs, many of which are not based on stretch reflexes. Strictly speaking, the term “spasticity” refers to an increase in excitability of muscle stretch reflexes, both phasic and tonic, that is present in most patients with an UMN lesion (9). Clinically, the defining characteristic of spasticity is excessive resistance of muscle to passive stretch. It is the nature of that resistance to increase as the examiner increases the velocity of stretch (10). Faster rates of stretch result in a sudden increase in resistance felt by the examiner after stretch has commenced. The afferent-efferent character of the stretch reflex was first identified in Sherrington’s seminal studies (11, 12) on the cat’s myotatic reflex which provided strong physiological underpinnings for later clinical descriptions of spasticity. The clinical character of spastic stretch reflexes is succinctly described by Peter Nathan (8): “Spasticity is a condition in which the stretch reflexes that are normally latent become obvious. The tendon reflexes have a lowered threshold to tap, the response of the tapped muscle is increased, and usually muscles besides the tapped one respond; tonic stretch reflexes are affected in the same way.” The quick whack of a tendon tap resembles an engineering impulse function and the resulting brevity of the jerk response aptly classifies it as a *phasic* reflex, based on its phasic (transient) output response. In contrast, longer duration passive stretch of a spastic muscle induces sustained tension for the duration of stretch and reflects underlying stretch reflex activity of the *tonic* type. Resistance perceived by the examiner is elevated in the spastic state and varies with the velocity of stretch. If resistance develops suddenly during rapid passive stretching, the act of passive stretch may be interrupted for an instant and the examiner will feel a “spastic catch” phenomenon. Clonus develops under similar circumstances.

Physiologically, afferent information regarding stretch of the muscle and its muscle spindle is signaled to the central nervous system by group Ia and group II afferents. However, there has been no evidence to suggest that spindle afferent activity is increased in spastic patients (13). Rather, the central excitatory state of the cord appears to be high (14). A number of theories of spasticity emphasize the concept of signal “mishandling” at the level of the spinal cord. For example, Delwaide points out that the normal mechanism of pre-synaptic inhibition in the spinal

cord is altered for patients with hyperreflexia (15). Ia afferent activity from the muscle spindle is normally adjusted at a pre-motoneuronal level depending on supraspinal facilitatory influences and preeding Ia discharges. In spasticity, according to Delwaide, the interneuron responsible for pre-synaptic inhibition becomes less active due to a reduction of supraspinal facilitatory influences. Accordingly, the stretch reflex of the patient with hyperreflexia is no longer subject to tonic inhibitory control by the mechanism of pre-synaptic inhibition. Instead, all proprioceptive afferent impulses are able to gain direct access to alpha motor neurons and hyperreflexia results. Other theories of signal “mishandling” at the level of the spinal cord include Veale, Mark and Rees’ work on Renshaw system disinhibition (16) and Jankowska’s work on abnormal handling of group II afferent activity from the muscle spindle by a specific interneuronal system in the spinal cord (17). What is common to these theories is an enhanced central excitatory state that promotes exaggerated motor responses to ordinary cord input.

Lance characterized spasticity as an increase in velocity-dependent *tonic* stretch reflexes along with exaggerated (*phasic*) tendon jerk responses (18). The term “phasic” means time varying. “Tonic” has a time invariant quality, though time scales are always relative. However, the literature’s use of ‘phasic’ and ‘tonic’ can be confusing because some authors describe the input stimulus as ‘phasic’ or ‘tonic’ while others describe the output response as ‘phasic’ or ‘tonic’. *Tonic* stretch reflexes discussed by Lance referred to the output response of a muscle group that was being stretched at different rates of stretch. The output jerk response of a tendon tap was an example of a *phasic* stretch reflex. At the bedside, phasic stretch reflexes are tested by tendon taps while tonic stretch reflexes are tested by passively stretching a muscle group through the full (available) range of motion, repeating this manouver a number of times in order to vary the velocity of stretch for each repetition. When a patient is spastic, resistance to stretch experienced by the examiner will increase as the rate of stretch is increased. Physiologically, an increase in electromyographic (EMG) activity generated by the stretched muscle is observed, producing tension that opposes the stretching force of the examiner. Figure 35-1 illustrates stretch reflex activity in a patient with traumatic brain injury (TBI) undergoing passive stretch of the elbow flexors at different rates of stretch. Although the examiner, as he stretches, feels a unitary resistance, the reader can see that different muscles may respond differently to the same input stretch. The reader may infer that differential muscle responses may have different treatment requirements.

Stretch reflex activity of antagonist muscles may also be triggered during voluntary movement when a shortening contraction produced by agonist muscles on one side of a joint is necessarily accompanied by lengthening

(stretching) of antagonist muscles on the other side of the joint. Paretic patients often move slowly so that velocity of stretch during voluntary effort is low enough to minimize spastic reactivity in antagonist muscles. In this regard, co-contraction is a phenomenon that can be confused with spasticity. Co-contraction is characterized by *simultaneous* activation of agonist and antagonist muscles during voluntary movement (19). Spasticity depends on muscle stretch and its onset occurs after movement has begun after some stretch displacement has already taken place. Simultaneous activation of agonists and antagonists is more easily observed on EMG records. (Figure 35-2)

## 2. CLONUS

Clonus is a low frequency rhythmic oscillation in one or more limb segments. (Figure 35-3) Clonus is generated by rapid stretch and hold of a muscle group. It may also be triggered by a patient who unintentionally stretches a

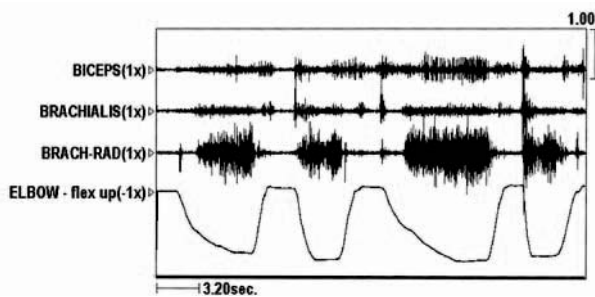


FIGURE 35-1

Passive stretch of elbow flexors performed by an examiner at different rates of stretch in a patient with TBI and UMN. As the velocity of stretch increases, more EMG is generated. Note, however, that different muscles respond differently to the same input

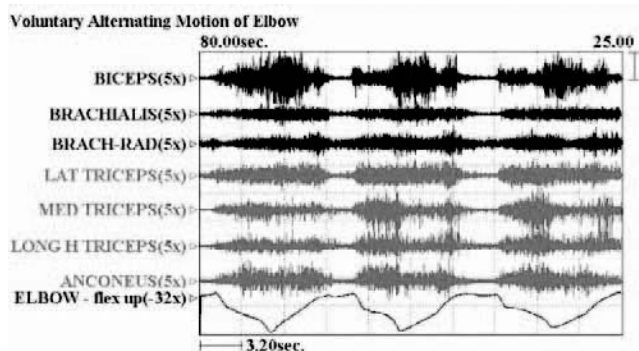


FIGURE 35-2

Co-contraction of elbow flexors and extensors during voluntary alternating movements at the elbow. The patient complained of fatigue and she felt as if she were "fighting herself" when she made these movements

muscle group during limb positioning (e.g. by mechanically stretching the calf when placing the foot on a wheelchair's footpedal). Clonus may be triggered during voluntary movement, for example, during a reaching effort when voluntary elbow extension triggers clonus in elbow flexors. Electromyographically, clonus is characterized by repetitive, rhythmic bursts of short duration electrical activity. Clonus occurs at typical frequencies of 6 to 8 Hz. Clonus can appear synchronously in one or more muscles. Clonus can also alternate between agonist and antagonist muscles. Figure 35-4 shows a patient with hemiparesis who was

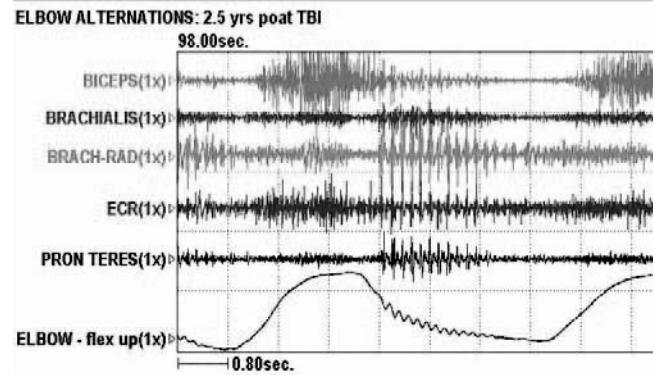


FIGURE 35-3

Illustration of clonus during extension phase of voluntary alternating movements of the elbow. Clonus is a low-frequency rhythmic oscillation, approximately 6-8 Hz, in one or more limb segments. This patient illustrates clonic bursts of EMG in brachioradialis, extensor carpi radialis, and pronator teres. The displacement trace reveals clonic oscillations of the elbow 'sitting atop' the extension phase of the movement

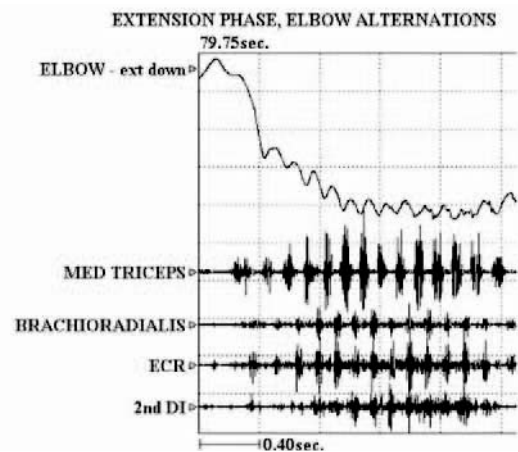


FIGURE 35-4

A patient with hemiparesis (gunshot wound of the brain) extends his elbow. Alternating bursts of clonic EMG activity are seen between medial triceps and brachio-radialis. Spread of activity to distal muscles (e.g., first dorsal interosseous) is also observed

asked to extend his elbow. Bursts of EMG can be seen to alternate between medial triceps and brachioradialis. In addition, spread of activity to more distal muscles (extensor carpi radialis and 1st dorsal interosseous) is also observed. Clonus may be sustained or unsustained and it can be stopped by re-positioning clonic muscles at shorter lengths. Clonus is usually associated with other hyperexcitable phasic stretch reflexes. In addition to rapid stretch, various cutaneous stimuli, especially cold or noxious stimuli, may give rise to ipsilateral or even contralateral clonus (20). Clonus may represent auto-oscillation of a hyperexcitable stretch reflex loop (21). Rack et al. viewed clonus as a self-sustaining oscillation of the stretch reflex pathway but they felt that the frequency of clonus was determined by physical parameters such as load rather than central neurological mechanisms (22). Dimitrijevic et al. were of the opinion that a central oscillator produced clonus (23). Therapeutically, dantrolene sodium, an agent that acts directly on skeletal muscle and muscle spindle fibers, is particularly effective for damping the low frequency ('low tone') oscillations of clonus. Unfortunately, it is not very effective in 'high tone' situations such as the high frequency drive of decerebrate rigidity after TBI.

### 3. CO-CONTRACTION

Co-contraction is another form of muscle over-activity seen in UMN that may be described as simultaneous activation of agonist and antagonist muscles during voluntary movement. Co-contraction can be activated and deactivated at a cortical level and is related to the switching mechanism of reciprocal inhibition in the cord (24). Abnormalities of Ia reciprocal inhibition have been reported for patients with UMN and co-contraction in such patients may represent an impairment of supraspinal control of reciprocal inhibition (25–27). Co-contraction may occur during isometric effort so that it is not necessarily related to muscle stretch. Figure 35-5 illustrates co-contraction during forward reach by an adult with UMNS. Simultaneous activation of flexors and extensors of the elbow is observed in the record. The movement trace reveals slow, unsmooth extension. Though co-contraction can be a normal mechanism to provide joint stability, in this case, the patient's elbow flexors appear to be exerting an unwanted restraining action because the patient struggled to extend his elbow clinically during reaching. Figure 35-5 reveals that brachioradialis and biceps activity occurred at the very onset of movement, indicating that early activity in these muscles was not stretch induced but was likely linked to the supraspinal reach "command". A key feature of co-contraction is that it is generated by simultaneous motor drive to agonist and antagonists during voluntary effort (28). When a co-contracting antagonist, undergoing stretch, develops superimposed spasticity, the combination has been called spastic co-contraction.

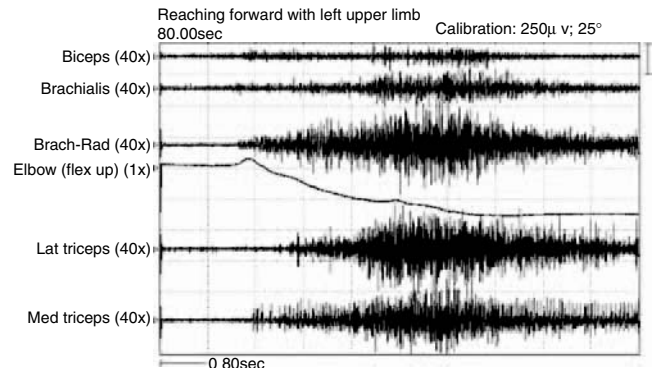


FIGURE 35-5

Co-contraction during forward reach by an adult with UMNS. Simultaneous activation of flexors and extensors of the elbow is observed in the record. The movement trace reveals a slow, nonsmooth extension trajectory (flexors restrain extensors)

Clinically, patients with co-contraction make slow, effortful movements. Speed of 'back' and 'forth' or alternating movement is often asymmetrical. For example, when a patient is asked to alternately flex and extend a limb, co-contraction of flexors during extension phase may prolong extension phase compared with flexion phase. We typically test for antagonist restraint by asking the patient to perform voluntary alternating movements about a joint for the full available range. Normally, alternating 'back' and 'forth' movements are symmetrical in time ('back' duration = 'forth' duration) and amplitude (endpoints or 'back' and 'forth' movements are at full range, respectively). Patients with restraining co-contraction, however, exhibit temporal and range asymmetries. Therapeutically, co-contracting antagonist muscles may respond to a weakening strategy (chemodenervation, tendon lengthenings). Among central muscle relaxants, only tizanidine has been described as having a potential effect on Ia reciprocal inhibition (29).

### 4. FLEXOR AND EXTENSOR SPASMS

According to Lance, a characteristic feature of UMN, both physiologic and clinical, is release of flexor reflex afferents (30). The flexor reflex, a polysynaptic reflex that results in flexor muscle contraction, is elicited by afferent stimuli collectively known as flexor reflex afferents. Among others, these afferents include exteroceptive cutaneous receptors responding to touch, temperature and pressure, nociceptors responding to painful stimuli, secondary endings from muscle spindles (group II afferents) and free nerve endings scattered ubiquitously over muscles that generate slowly conducting afferent activity in group III and IV axons. The polysynaptic flexor reflex has a prolonged latency (more than twice that of a monosynaptic tendon jerk) due to slow afferent conduction to the

cord and also to central delay. In the cord, flexor reflex afferent activity travels up and down to synapse in the internuncial pool, a system of spinal interneurons that is influenced by inputs coming from peripheral as well as central sources including the brainstem. Compared to segmental stretch reflexes, the time course of polysynaptic flexor reflexes is slower and, unlike segmental stretch reflexes, flexor reflexes represent coordinated activity of motoneuron pools spanning many segments, resulting in muscle contraction across several joints, sometimes bilaterally. By typically recruiting flexor muscles across several joints, the flexor reflex is an example of an interjoint reflex that has tissue protective value such as enabling quick withdrawal from a noxious stimulus. Extensor reflexes are also polysynaptic and interjoint in nature and may serve certain support functions. Flexor and extensor reflexes may be core substrate for more complex coordinated patterns such as locomotor stepping generators.

After UMN, particularly after spinal cord lesions, release of inhibitory descending influences makes reflexes such as the flexor reflex more pronounced. When complaints are traced to flexor and extensor spasms, it is likely that spasms represent disinhibited flexor and extensor reflexes. A variety of overt stimuli can trigger flexor and extensor spasms or they may be set off by covert stimuli such as a full bladder, a stool distended bowel, a tight diaper, unseen skin ischemia from sitting or lying in one position too long and other unobserved or masked sensory sources.

Clinically, flexor reflexes can range from the familiar toe response of the Babinski sign to a mass flexor reflex characterized by intense, often painful interjoint flexion with spread to the abdominals. Patients may call them a muscle spasm but they mean whole limb involvement rather than focal spasm of a single muscle group. In UMN lesions, the elicitation threshold of the flexor reflex is reduced, the intensity of muscle contraction for the same stimulus input is increased and interjoint components of the reflex are often expanded (i.e. more muscles and more joints are recruited). Drugs such as baclofen and diazepam can inhibit polysynaptic activity in the cord and reduce the frequency and intensity of flexor spasms (but in TBI they may sedate (baclofen and diazepam) or affect memory (diazepam)). Excessive flexor withdrawal on ground contact can impair stance phase of gait for patients with TBI. Excessive flexion during swing phase can mimic steppage and impair advancement or subsequent foot placement on the floor.

## 5. SPASTIC DYSTONIA

The term 'spastic dystonia' originated with Denny-Brown (31). He examined postural reactions of monkeys after cerebral cortex ablations. Lesions were independent of,

or in addition to, damage to the pyramidal tract. When the bodies of animals with cortical ablations were held in different positions, their limbs developed fixed positions or postures. For all postures, any attempt by the examiner to pull the limb away from its fixed position was met by an increasing resistance of spring-like quality. The limb would 'fly' back to its original posture when released. Denny-Brown called this fixed attitude *dystonia*, meaning that the fixed limb posture was maintained by *active muscle contraction*. The continuous nature of muscle contraction that maintained cortical dystonia was present without the monkey making limb or body movements elsewhere and the dystonia did not depend on afferent input from the limb, since it persisted even after the relevant dorsal roots were cut. Moreover, EMG recordings of dystonic monkey muscles revealed sustained or tonic EMG activity and Denny-Brown thought that dystonia of this kind represented release of motor mechanisms that had direct access to alpha motoneurons. What seems clear, therefore, is that these dystonic postures were mediated efferently from above and had nothing to do with spinal reflex activity. However, what is not clear to these authors is the exact meaning of the term: 'spastic dystonia'. Denny-Brown himself pointed out that there were dystonic monkeys without spastic features such as increased tendon jerk reflexes. Nevertheless, he indicated that dystonia may occur in the presence of spasticity (enhanced phasic and tonic stretch reflexes) He referred to such a combination as "spastic dystonia". Many clinicians seem to use the term 'spastic dystonia' when they see a UMN patient with fixed limb postures (e.g. flexed elbow, clenched fist) in the absence of obvious stretch or voluntary effort. It is not clear, however, just from visual observation that a fixed posture is driven by sustained, supraspinal efferent activity—a necessary requirement of the term 'spastic dystonia'. We prefer to use the term when such a patient has tonic muscle activity, demonstrated by EMG, that maintains the limb in a fixed posture in the absence of phasic stretch or voluntary effort. Spastic dystonia is primarily due to abnormal supraspinal drive, characterized by an inability to inhibit muscle activity despite efforts to do so. Gracies et al. state that spastic dystonic muscles are sensitive to the degree of tonic stretch imposed on them (32). Figures 35-6 and 35-7 show a patient with right hemiparesis due to a brain gunshot wound who was asked to stand quietly 'at rest'. EMG recordings showed tonic activity in biceps and occasional activity in brachioradialis. Flexion posture of the elbow was persistent, the patient was not making a voluntary effort to hold the position nor was he undergoing phasic (time varying) stretch. Clinically, the patient had signs of spasticity. One might describe this patient as having 'spastic dystonia'. In Denny-Brown's sense of mechanism for this phenomenon, tonic biceps activity comes from supraspinal drive of alpha motoneurons. This is not so easy

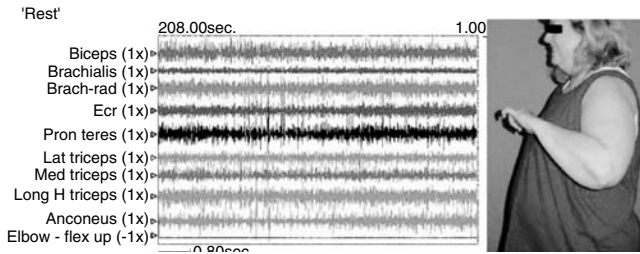


FIGURE 35-6

Spastic dystonia. This patient with an upper motoneuron syndrome and left hemiparesis was asked to stand quietly "at rest." The flexed posture of the elbow was persistent, and the patient readily acknowledged that she was not making any voluntary effort to hold this position. Persistent elbow flexion was her chief complaint. An EMG record during "rest" revealed persistent activity in many muscles about the elbow and forearm

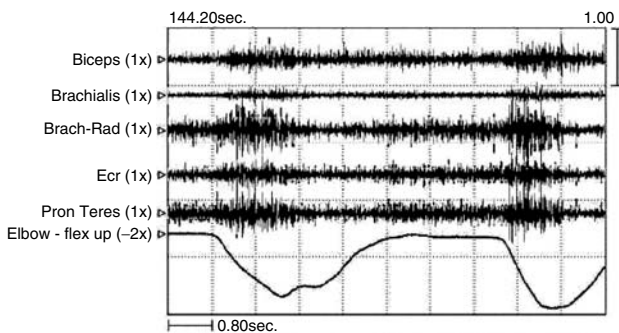


FIGURE 35-7

Passive stretch of the elbow flexors of the patient in Figure 35-6 revealed that her dystonic activity was stretch-sensitive. According to Denny-Brown, the dystonic phenomenon (activity at rest) is of supraspinal origin and is mediated efferently, not afferently. However, the presence of stretch sensitivity suggests that some patients may also have a component of spasticity

to prove, yet its assertion has therapeutic implications. For example, one would not expect central agents such as diazepam and baclofen, known to suppress spinal reflex activity, to be very useful for treating 'spastic dystonia'. Focal chemodenervation by botulinum toxin, neurolysis by phenol or direct contraction inhibition by dantrolene would seem to have stronger therapeutic rationales.

EMG equipment, if available, can help identify persistent muscle activity that may be consistent with a dystonic form of muscle overactivity. Without such study, clinical assumptions about the mechanism of a limb posture may be risky. A net balance of force created by passive tissue stiffness may be sufficient to maintain limb posture. Contracture can hold a limb in fixed position

as can heterotopic ossification. Finally, associated reactions can generate limb muscle activity that ends in postures reflecting a net balance of muscle forces acting across various joints.

## 6. ASSOCIATED REACTIONS

Associated reactions were first described by Walshe in 1923 as 'released postural reactions deprived of voluntary control' (33). 'Synkinesis' is a term used by Bourbonnais more recently (34). An associated reaction refers to involuntary activity in one limb that is associated with a voluntary movement effort made by other limbs. Associated reactions may be due to disinhibited spread of voluntary motor activity into a limb affected by a UMN lesion. Figure 35-8 shows a patient with left hemiparesis due to a brain gunshot wound attempting to readjust his sitting position by pushing down on the wheelchair's armrest with his right arm. The patient was unable to use the left upper extremity in this task because voluntary control was severely impaired. Dynamic EMG of elbow musculature during this activity revealed high EMG recruitment in flexor and extensor muscles about the elbow (figure 35-9). Despite elbow extensor activity, the photograph reveals *flexed* elbow posturing indicating that a net balance of muscle forces about the elbow favored flexion. The intensity of an associated reaction may depend upon how much voluntary effort is made. Dewald and Rymer thought that impaired descending supraspinal commands were involved in generating associated reactions (35). They hypothesized that unaffected bulbospinal motor pathways may have taken over the role of damaged UMN tracts during the transmission of descending voluntary commands.

Assuming that associated reactions are supraspinal in origin, one would not expect efficacy from central relaxants such as baclofen and diazepam. Depending on the contractile intensity of an associated reaction, dantrolene sodium, an inhibitor of muscle contraction, might have some therapeutic value. Tizanidine has known effects at spinal levels, but it may also act supraspinally by influencing activity in descending coeruleospinal pathways. Reports of depressed neuronal activity in the locus coeruleus by alpha-2 adrenergic agonist drugs have emphasized their impact on cord mediated reflexes such as flexor reflexes but not on supraspinally mediated behaviors such as associated reactions (36). The authors are not aware of reports regarding tizanidine and associated reactions in man.

The 'real life' impact of spasticity, strictly defined, may be less than advertised when one reflects on how often patients and caregivers might actually stretch spastic muscles at rates that would elicit intense spastic responses. We have commonly observed patients and



FIGURE 35-8

An “associated reaction” refers to involuntary activity in one limb that is associated with a voluntary movement effort made in other limbs. This figure illustrates an associated reaction in the left arm of a patient with left hemiparesis (gun-shot wound of brain) who is readjusting his sitting position in the wheelchair by volitionally pushing down on the arm-rest with his right arm. The patient was unable to use the left upper extremity in this task because voluntary motor control was severely impaired on the left

caregivers performing limb manipulations at slow rates of stretch in order to avoid or minimize rate sensitive spastic resistance. In addition, what frequently passes for dynamic spastic resistance may be, in large measure, an increase in static stiffness due to intrinsic changes in the physical properties of muscle tissue. By contrast, frequent occurrence of associated reactions may be unavoidable in ‘real life’ situations because voluntary movement made by ‘uninvolved’ limbs happen all the time. High intensity voluntary efforts required during transfers, gait and activities of daily living might be expected to promote associated reactions as a high frequency form of muscle overactivity. For patients with UMN, it is conceivable that the everyday potential for generating associated reactions may contribute to the development of muscle stiffness and contracture more than spasticity does. More studies along this line would help.

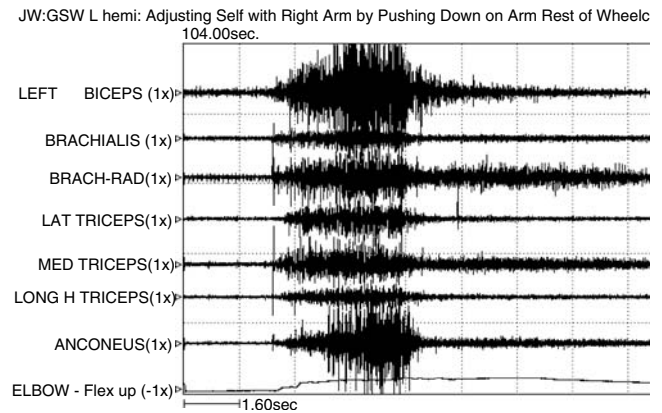


FIGURE 35-9

Dynamic EMG study of elbow musculature in the patient of Figure 35-8 was performed during the same manoeuvre of re-adjusting position in the wheelchair. Findings revealed high EMG recruitment for flexor *and* extensor muscles about the elbow. Despite elbow extensor EMG activity, the photograph in Figure 35-8 reveals *flexed* elbow posturing indicating that, despite extensor muscle contraction, a net balance of muscle forces about the elbow favored flexion posturing. The intensity of a limb’s associated reaction may depend on the magnitude of voluntary effort made by the patient elsewhere

## 7. MUSCLE STIFFNESS AND CONTRACTURE

Muscle contracture refers to physical shortening of muscle length and it is often accompanied by fixed shortening of other soft tissues such as fascia, nerves, blood vessels and skin. Muscle *contracture*, an invariant physical state of fixed shortening, should not be confused with muscle *contraction*, a dynamic, variable state of internal shortening produced by sliding action of actin and myosin filaments within a muscle fiber. The development of contracture is promoted by a number of processes that start when an acute UMN lesion occurs: paresis impairs cycles of shortening and lengthening of agonist and antagonist muscles promoted by everyday muscle usage, the force of gravity generates positional effects on limb segments and joints, positional effects are created by a net balance of static rheologic forces across joints, and, as preferential muscle overactivity develops in particular muscle groups, a net balance of dynamic contractile forces promotes positional effects leading to contracture. Contracture implies that even if one blocked all muscle *contraction* by local or general anesthesia, physical shortening of muscle would still remain. Since central muscle relaxants such as tizanidine and baclofen, peripheral agents such as dantrolene, chemodenervation/neurolytic agents such as botulinum toxin/phenol affect dynamic muscle contraction only, a clinical picture dominated by contracture will not respond to these types of interventions. Physical and surgical methods are necessary to undo contracture.

**TABLE 35-1**  
***Common Patterns of Upper Motoneuron Dysfunction, Potential Muscles Involved and the Authors' Botulinum Toxin Dose Ranges***

The Adducted/Internally Rotated Shoulder	Flexed Hip		
Flexed Elbow	Scissoring Thigh(s)		
Pronated Forearm	Stiff Knee		
Bent Wrist	Flexed Knee		
Clenched Fist	Equinovarus Foot with Curl or Claw Toes		
Thumb-in-Palm	Valgus Foot		
Intrinsic Plus Hand	Hitchhiker's Hyperextended Great Toe		
CLINICAL PATTERN	POTENTIAL MUSCLES INVOLVED	BOTOX ® A DOSE UNITS/VISIT	# INJECTION SITES
<i>Upper Limb</i>			
Adducted/Internally Rotated Shoulder	Pectoralis major	60-120	3
	Latissimus dorsi	80-160	4
	Teres major	25-50	1
	Subscapularis	20-50	1
Flexed Elbow	Brachioradialis	40-80	2
	Biceps	60-120	4
	Brachialis	30-60	2
Pronated Forearm	Pronator teres	25-50	1
	Pronator quadratus	20-40	1
Flexed Wrist	Flexor carpi radialis	30-60	2
	Palmaris longus	30-40	1
	Flexor carpi ulnaris	20-30	1
	Extrinsic finger flexors	40-80	4
Thumb-in-Palm	Flexor pollicis longus	20-30	1
	Flexor pollicis brevis	10-15	1
	Adductor pollicis	10-15	1
Clenched Fist	Various muscle slips FDP	40-80	4
	Various muscle slips FDS	40-80	4
Intrinsic Plus Hand	Dorsal Interossei	40	4
	Lumbricales	40	4
<i>Lower Limb</i>			
Flexed Hip	Iliacus	50-100	1
	Rectus femoris	75-150	3
Flexed Knee	Medial hamstrings	50-150	2
	Lateral hamstrings	50-150	2
Adducted Thighs	Adductor longus	50-100	2
	Adductor magnus	50-100	2
Stiff (extended) Knee	Rectus femoris	50-150	3
	Vastus lateralis	25-50	1
	Vastus medialis	25-50	1
	Vastus intermedius	25-50	1
Equinovarus Foot	Medial gastrocnemius	25-75	2
	Lateral gastrocnemius	25-75	2
	Soleus	25-75	1
	Tibialis posterior	25-75	1
	Tibialis anterior	25-75	2
	Flexor digitorum longus	20-50	1
Hitchhiker's (Striatal) Toe	Extensor hallucis longus	20-50	1
	Extensor hallucis longus	20-50	1

After a UMN lesion, paralyzed muscles immobilized for long periods in a shortened position became shortened and stiffer. When muscle overactivity develops in these shortened muscles, tension is generated at shorter lengths. A lack of voluntary contraction in the antagonists of these shortened muscles prevents their natural re-extension, leading to a continuation of the process of stiffness and fixation. In the upper limb, for example, muscles that typically shorten include shoulder adductors and internal rotators, elbow flexors, forearm pronators, wrist, finger and thumb flexors and thumb adductors. However, other patterns are possible and observed. Familiar UMN patterns of deformity develop in both the upper and lower limbs (Table 35-1) (figures 35-10 and 35-11). The position of a given joint results from a net balance of static and dynamic muscle forces acting across one or more joints. Literature support of this idea comes from many studies. Herman described changes in the rheologic properties of spastic muscles in a large number of hemiplegic patients (4). Patients with contracture often had *reduced* reflex activity, yet resistance to passive stretch was high because muscle tissue had become physically more stiff. His study indicated that a description of muscle tone must consider the complex interaction between rheologic and reflex properties of muscle because stretch reflex properties of spastic muscle may be influenced considerably by alterations in the physical properties of muscle. Along similar lines, Dietz et al. (5) (stroke, cerebral palsy) and Thilmann et al. (37) have argued that hypertonia might not be related to exaggerated reflexes but rather to changes in soft tissues. Hufschmidt and Mauritz (38) proposed that abnormal cross-bridge connections could contribute to the resistance of passive movement and that these changes would very likely occur in muscles subjected to prolonged positioning. Akeson (39) demonstrated in animals that immobility led to stiffness associated with water loss and collagen deposition and Gossman (40), Herbert (41), Carey and Burghardt (42) have suggested that immobility imposed on a patient by the negative signs of UMN can result in soft tissue contracture. Other animal studies have suggested that when muscles are immobilized in a shortened position, some sarcomeres are lost and others become shorter and stiffer (Tabary (43); Williams and Goldspink (44); Witzmann (45)). Soft tissues other than muscle become less compliant in chronically shortened positions. It is for this reason that surgery for a severe contracture should not corrected for more than about half the lost range for fear of snapping nerves and occluding blood vessels. These soft tissues will require gradual physical stretching techniques postoperatively to achieve reversal of the second half of the range. Special surgical intervention for skin contracture may also be required.

Human biopsy studies of muscle with contracture have shown shorter fiber lengths for patients with cerebral



FIGURE 35-10

A familiar UMN pattern of upper limb deformity: adducted/internally rotated shoulder; flexed elbow; pronated forearm; bent wrist; clenched fist; thumb-in-palm. The position of a given joint results from a net balance of static and dynamic muscle forces acting across one or more joints that are promoted by a variety of UMN phenomena that are triggered frequently, likely every day (e.g., spasticity, co-contraction, flexor and extensor spasms, associated reactions)

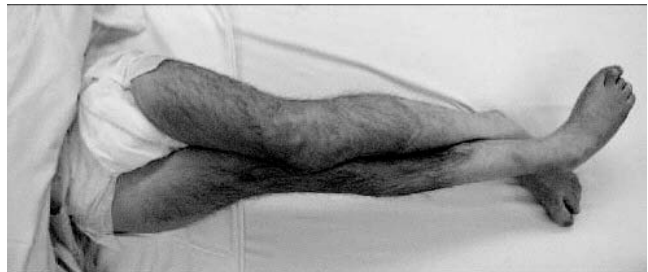


FIGURE 35-11

A familiar UMN pattern of lower limb deformity: flexed hip, adducted (scissoring thighs); flexed knee; stiff knee; equinovarus foot

palsy compared to normal (46). Shorter fiber lengths would have fewer sarcomeres in series. When antagonist muscle fibers with fewer sarcomeres are stretched during normal agonist concentric contraction, stretched sarcomeres become longer, compared with sarcomeres of normal fibers. During stretch, these longer than normal sarcomeres are thought to be the main reason that many patients with cerebral palsy have excessive passive tension in their muscles. A similar process might conceivably account for elevated passive tension in adults with UMN lesions. A different finding was recently described by Friden and Lieber (47) who found that single fibers taken from spastic subjects with cerebral palsy developed



passive tension at significantly shorter sarcomere lengths than fibers taken from subjects without spasticity. Patient fibers were almost twice as stiff as controls and resting sarcomere lengths were shorter. Friden and Lieber found that the force borne by spastic fibers was similar to normal fibers, even though the cross-sectional area of spastic fibers was less than one third of normal fibers. Greater stress resulted when spastic fibers were passively stretched. Their study suggested that sarcomeres in subjects with cerebral palsy do not have to be stretched beyond normal lengths to develop excessive passive tension. From this perspective, their study challenged the assumption that tendon lengthenings or even stretching exercises that aim to allow a muscle to relax to normal sarcomere lengths will lessen passive tension to normal levels. Their study challenges the current theoretical framework which suggests that when muscle-tendon length is adjusted appropriately, sarcomeres will operate over a more normal range of lengths and there will be a reduction in passive tension and an increase in active force potential. Their study of chronic spastic muscle fibers (during childhood development) points to a process of considerable intrinsic structural remodeling of muscle tissue components that may not be easily reversed by current surgical or physical manipulations.

#### GENERAL COMMENTS ON THE APPROACH TO EVALUATION

*Clinical Aspects of Evaluation* In broad terms, evaluation of muscle overactivity focuses on three issues: (1) identifying the clinical pattern of motor dysfunction; (2) identifying the patient's ability to control muscles involved in the clinical pattern; and (3) identifying the role of muscle stiffness and contracture as it relates to the functional problem. In Table 15-1, we identify fourteen common patterns of motor dysfunction, organized by joint or limb segment, that are typically found in patients with TBI who have upper motor neuron lesions. For each pattern, a number of muscles may be involved in motor dysfunction. Evaluation focuses on the characteristics of these muscles in terms of their voluntary or selective control, type of muscle overactivity, rheologic stiffness and contracture. Does the patient have voluntary control over a given muscle? What is the nature of a muscle's overactivity? (e.g. Is the muscle spastic? Does the muscle co-contract? Is it dystonic? Is it part of an associated reaction?) Does the muscle have increased stiffness when slowly stretched? Is contracture present? There are two or more muscles that cross each axis of most limb joints and each muscle can vary in its UMN characteristics. Since each muscle may contribute to movement of its joint, information about each muscle's contribution is useful to the assessment as a whole. We use dynamic electromyography to identify the characteristics

of muscle overactivity and voluntary control during upper and lower limb movements. We use anesthetic nerve blocks to identify properties of stiffness and contracture in particular muscle groups.

*Technology Aspects of Evaluation* Laboratory measurement of upper and lower extremity motion is a cornerstone of modern analysis of muscle overactivity and impaired voluntary control of movement. Gait and motor control analysis of movement is capable of measuring specific contributions of muscles to movement by means of multi-channel electromyography (dynamic EMG). Dynamic EMG is measured simultaneous with joint motion (kinematics) and ground reaction forces (kinetics). Force platforms enable the measurement of ground reaction forces during walking and standing and permit force vector analysis. Computations based on photo marker systems allow collection of three-dimensional quantitative motion data that provide information regarding range, direction, velocity and acceleration of limb movements. Clinical correlations and interpretations are significantly enhanced by slow-motion video that provides frame-by-frame display of walking and other limb movements. Measurement of passive movement responses combined with pre- and post-nerve block data allow for clinical interpretations of tone and contracture. What is abundantly clear, especially after TBI, is that clinical examination alone may be insufficient to identify voluntary and muscle overactivity characteristics of the many muscles impaired by UMN. Combined with clinical information, laboratory measurements provide the degree of detail necessary to generate practical hypotheses about findings that lead directly to the formulation of rational treatment interventions.

*Considerations Related to Time Course of Motor Recovery* Evaluation and treatment will also depend on a clinician's expectation for motor recovery. We arbitrarily divide neurological recovery into two periods: an early period during which neurological motor recovery may be expected and a late period when motor recovery for all practical purposes has ended. In our experience, practical UMN motor recovery after head injury winds down significantly between six and twelve months after injury. Functional recovery is a different story. Even if many years have elapsed after a head injury, interventions aimed at improving function can produce practical changes. For example, a non-ambulatory patient whose base of support is severely compromised by equinovarus deformity during stance phase may regain ambulation through neuro-orthopaedic re-balancing of muscles crossing the ankle joint that change the base of support. Functional recovery may occur at any time after head injury provided that compensatory interventions are feasible and the patient has sufficient motor control to take advantage of the changes in biomechanical conditions.

*Clinical Commentary on Treatment Perspectives* Before 1980, little heed was given to cognitive, behavioral and psychosocial aspects of head injury. Patients with severe disability after TBI were not considered candidates for rehabilitation. Those with lesser disability who were admitted to a rehabilitation center were given physical rehabilitation, based on approaches used for patients with stroke and spinal cord injury. The pendulum shifted in the next decades toward cognitive and behavioral aspects of TBI as professionals began to recognize that families were more vulnerable to the burdensome effects of impaired behavior and cognition than they were to the effects of physical impairment (48). With a relatively reduced emphasis on physical rehabilitation, treatment of muscle overactivity was approached less aggressively. Drugs used in spinal cord injury and multiple sclerosis such as diazepam, baclofen and dantrolene were looked upon cautiously because of their sedating, fatiguing and weakening side effects. Surgery was typically based on inferences made from physical examination alone and was considered an option of last resort, often focused on reduction of severe deformity rather than increasing functional performance. Surgeons were not well acquainted with cognitive and behavioral issues that might affect their pre-operative decisions and post-operative care. Rehabilitation staff who dealt with cognitive and behavioral issues generally thought that surgery was an aggressive choice of last resort. Many nonsurgical physicians thought so too — especially since the experience of local surgeons with an interest in neurological problems varied greatly.

We believe that good conservative and surgical methods are available for improving function of patients with muscle overactivity. Psychosocial considerations and time course of motor recovery are important in the planning process. Most importantly, we emphasize focal analysis of muscles, joint by joint, that exhibit positive and negative signs of UMN because UMN pathology is highly variable. When TBI produces UMNS, the degree of voluntary function that remains varies greatly from muscle to muscle, even in the same limb segment. Factors related to poor production and regulation of movement need to be distinguished from those that reflect different forms of muscle overactivity along with rheologic changes. These distinctions may be based on physical examination alone but technology-based evaluations provide increasingly useful and objective support to complement clinical analysis. Treatment of motor dysfunction associated with UMNS is linked not only to muscle overactivity but also to concepts of voluntary production and control of movement along with rheologic change.

## PATTERNS OF UMN MOTOR DYSFUNCTION

The varied forms of muscle overactivity in UMN lead to familiar postures of upper and lower extremity joints by

virtue of a net balance of contractile and rheologic forces generated in time. Many common patterns have been presented in Table 35-1. We now expand them in bullet format below. The remainder of the chapter adds discussion of central muscle relaxants, chemodenervation and neurolysis. Finally, a special section on neuro-orthopaedics allows the reader to gain greater familiarity with this approach through details of the operative techniques it employs.

### The Adducted, Internally Rotated, Flexion Restricted Shoulder

#### *Description, Functional Consequences and Penalties*

- S&S (signs and symptoms): shoulder adducted and internally rotated; some patients have hyperextension as their main problem; painful passive stretching of adductors is a common complaint
- PF (passive function): axillary redness, maceration and skin breakdown may be present; restriction of access to axilla for washing and hygiene is problematic for caregivers and patients
- AF (active function): some shoulder adductors are also shoulder extensors so, depending on the net balance of shoulder muscle forces, impaired voluntary flexion, abduction and rotation of the shoulder can make whole limb actions such as reaching, pushing, stabilizing and otherwise placing the hand in space problematic; difficulty raising the arm and placing the hand behind and on top of the head is common

#### *Differential Diagnosis and Diagnostic Work Up*

- Muscles that may contribute: adduction &/or internal rotation: pectoralis major (PM), teres major (TM), latissimus dorsi (LD), anterior deltoid (AD), subscapularis (SC); hyperextension or flexion restricting: long head of triceps (LHT), teres major, latissimus dorsi, posterior deltoid (PD)
- Taut tendons of PM, TM and LD palpable in the axilla; resistance to passive abduction, external rotation and extension of shoulder is typically high and often painful
- Restricted motion from capsular tightness needs to be distinguished from increased muscle resistance; examine passive internal and external rotation with humerus at side of thorax and with humerus abducted
- Single voluntary movements: when passive exceeds active range for abduction, abductor weakness or adductor over-activity is suggested; when passive exceeds active flexion range, flexor weakness or extensor over-activity is suggested; when passive

exceeds active external rotation range, external rotator weakness or internal rotator over-activity is suggested

- Alternating (to and fro) movements: if voluntary abduction is slower than adduction, voluntary flexion is slower than extension, voluntary external rotation is slower than flexion, then weakness of abductors, flexors, external rotators and/or over-activity of adductors, extensors, internal rotators may be present
- With so many muscles potentially weak or overactive, dynamic EMG helps supplement clinical exam
- Radiographs should be obtained to rule out restricted motion caused by heterotopic ossification
- Local anesthetic blocks may clarify sources of restriction (muscles, over-activity, contracture): motor point blocks for PM, TM, LHT AD, PD; thoracodorsal nerve block for LD; access to SC is very difficult

### *Findings and Treatment Options*

- Unmasked voluntary shoulder flexion and/or abduction and/or external rotation after diagnostic blocks improves prospects for placing the hand in space, especially for reaching
- Consider chemodenervation with botulinum toxin and/or neurolysis with phenol
- Use of phenol for large muscles (e.g. LD, PM) offsets the need to use large doses of botulinum toxin in such muscles, thereby preserving the use of toxin for many smaller, more distal muscles; PM, TM, LHT, AD, PD are amenable to both chemodenervation and neurolysis
- Limited change in range of motion after local block suggests muscle contracture and/or capsular tightness
- Drugs for pain and blocks for over-activity may help an aggressive range program for focal contracture

### **The Flexed Elbow Deformity**

#### *Description, Functional Consequences and Penalties*

- S&S: riding up during standing and walking; fist and fingers may contact throat or face; pain on passive stretching
- PF: reddened, macerated elbow crease, skin breakdown; caregiver has difficulty with dressing, bathing; impact on balance during gait
- AF: restrained elbow extension during forward reaching; bringing objects to and from body is impaired

#### *Differential Diagnosis and Diagnostic Work Up*

- Muscles that may contribute to this deformity include: biceps, brachialis, brachioradialis and pronator teres and extensor carpi radialis

- Resting posture: elbow flexed, forearm more often pronated than supinated; ECR and PT may contribute when wrist is flexed, forearm pronated; an acutely flexed elbow can lead to stretch injury of ulnar nerve
- Very slow passive stretch establishes the available range of motion and the likely presence of contracture (fixed shortening)(Figure 35-12). Changing the velocity of stretch from slow to fast helps identify presence of spasticity. Ashworth test for spasticity: take joint through fully available passive extension in about one second. Brachioradialis and biceps contractions, when present, are easily observed. Much more difficult to ascertain brachialis contribution. Dynamic EMG is useful
- When “single” joint voluntary extension movements fall short of the available passive range of motion, flexor overactivity is likely but extensor weakness and changes in physical stiffness of flexors must be considered
- When patient is able to do alternating voluntary movements of flexion and extension, timing and amplitude asymmetries can be identified. When extension movements are visibly longer in time than flexion movements, overactivity of flexors is likely, but extensor weakness and flexor stiffness may be factors. Amplitude asymmetries have similar implications. In addition, contracture may be present
- An effort to move the limb as a whole as in reaching for an object or pushing a door may exhibit flexor or extensor synergy (pattern overlay), either partly or fully. Pattern overlay, a centrally generated phenomenon, may be less amenable to relief by peripheral interventions



**FIGURE 35-12**

Example of an elbow flexion contracture. Very slow passive stretch establishes the available range of motion and the likely presence of contracture (fixed shortening). Contracture is a physical phenomenon and requires physical methods of treatment such as aggressive stretching, serial casting or surgical lengthening

- Radiographs are obtained when bony block and heterotopic ossification is suspected
- Musculocutaneous nerve block in the axillary region can help differentiate role of muscle over-activity versus contracture of biceps and brachialis. A separate motor point block of brachioradialis is required to determine its role. Flexor blocks may unmask voluntary extension

### Findings and Treatment Options

- If range of motion improves completely after nerve blocks, muscle over-activity without contracture is likely the cause of the posturing
- An x-ray positive form H.O. establishes a mechanical block as likely source of motion impairment. Underlying motor control may be established using dynamic EMG (even if motion is not present) because the patient can produce alternating voluntary recruitment patterns in flexors and extensors respectively if they have good motor control
- Partial improvement in range or no improvement suggests contracture
- Serial casting may be considered, preceded by local anesthetic block or phenol block if a dynamic component has been established by maneuvers described above
- In the early period of recovery, serial casting, phenol blocks of musculocutaneous nerve and motor point of brachioradialis may be considered. Botulinum toxin is useful for biceps, brachioradialis and brachialis, even pronator teres and ECR can be elbow flexors by reverse origin and insertion
- Treating elbow muscular should be accompanied by treatment of shoulder, wrist and finger muscles, as necessary, as the limb should be thought of as a whole

### The Pronated Forearm

#### Description, Functional Consequences and Penalties

- S&S: forearm pronates excessively at all times; passive stretching may be painful
- PF: may be difficult to passively supinate palm for washing, fingernail clipping due to tight pronators
- AF: impaired voluntary underhand reaching; patient has difficulty orienting hand to objects

#### Differential Diagnosis and Diagnostic Work Up

- Muscles that may contribute: pronator teres (PT) and pronator quadratus (PQ)

- Resting posture: forearm is pronated, elbow typically flexed by flexor muscles including pronator teres
- Very slow passive stretch establishes the available range of motion and the likely presence of pronator contracture. Since PT crosses the axis of rotation of the elbow, an extended elbow may increase tension in pronator teres. Stretching the pronators by passive supination at different velocities helps identify presence of spasticity. Tension in PT is clinically palpable but PQ is not palpable. Dynamic EMG is useful (Figure 35-13)
- When voluntary supination movement falls short of the available passive range, pronator over-activity is likely but supinator weakness and changes in physical stiffness of pronators must be considered
- When a patient is able to do alternating voluntary pronation and supination movements, timing and amplitude asymmetries can be identified. When supination movements are visibly longer in time than pronation movements, over-activity of pronators is likely, but supinator weakness and pronator stiffness may be factors. Amplitude asymmetries may also suggest pronator contracture
- Radiographs are obtained to rule out bony block, especially if forearm fractures have occurred
- MP blocks of PT and PQ (through the interosseous membrane) can be performed to distinguish between intense muscle over-activity and contracture but not usual to do so

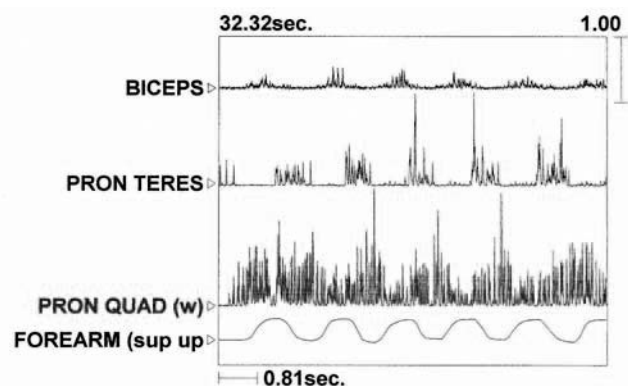


FIGURE 35-13

Dynamic EMG study of pronation/supination of the forearm. This patient with TBI complained of difficult reaching underhand. The record shows good reciprocal innervation of biceps and pronator teres. When the biceps is active as a forearm supinator, pronator teres is inactive. When the pronator teres is active as a forearm pronator, the biceps is inactive. The same cannot be said of pronator quadratus, which is active during pronation *as well as* supination. These findings are consistent with co-contraction phenomenon in pronator quadratus but not pronator teres. Treatment implication: focal chemodenervation or surgery should be aimed at pronator quadratus, not pronator teres

- Dynamic EMG helps identify patterns of weakness in supinators and overactivity in pronators

#### *Findings and Treatment Options*

- When dynamic EMG suggests overactivity in PT and/or PQ and contracture is mild or absent, consider chemodenervation with botulinum toxin
- When contracture is present, chemodenervation combined with serial casting can be used but casts must go above elbow and include the wrist
- When neurological recovery is no longer expected, consider surgical lengthening of PT and PQ

### **The Flexed Wrist Deformity**

#### *Description, Functional Consequences and Penalties*

- S&S: wrist flexed excessively; passive stretching may be painful; pressure in carpal tunnel may lead to carpal tunnel syndrome
- PF: redness and possible skin breakdown in wrist crease; may create difficulty for caregivers during dressing
- AF: impaired wrist extension during reaching; ulnar deviation may be present

#### *Differential Diagnosis and Diagnostic Work Up*

- Muscles that may contribute: flexor carpi ulnaris (FCR), palmaris longus (PL), flexor carpi ulnaris (FCU), flexor digitorum sublimis and profundus, extensor carpi ulnaris (ECU) (consider when ulnar deviation is present), wrist extensors (weak)
- Wrist range examined with elbow extended to maximize flexor stretch (& simulate what would occur during a full reach)
- Since extrinsic finger flexors as well as wrist flexors can provide stretch activated flexion forces across the wrist, their respective contributions are sorted out by passive extension of the wrist with fingers held flexed by the examiner and with fingers held extended
- Passive stretch: bowstringing of FCR is common, PL often involved as is FCU; resistance to stretch is enhanced by holding elbow in maximum available extension; passive abduction with wrist in neutral reveals stretch activity in ulnar deviators (FCU and ECU); when resistance to passive extension of the wrist is enhanced by simultaneous finger extension, extrinsic finger flexor spasticity also contributes to the wrist flexion deformity
- Dynamic EMG is helpful in identifying whether wrist flexor overactivity and/or wrist extensor

under-activity is present during reaching and whether overactivity is present in superficial or deep finger flexors or in both

- When selective voluntary extension of the wrist falls short of the available passive range of motion, flexor over-activity is likely but extensor weakness and flexor physical stiffness may be factors
- When a patient is able to do alternating voluntary flexion and extension, timing and amplitude asymmetries can be identified. When extension movements are visibly longer in time than flexion movements, over-activity of flexors is likely, but extensor weakness and flexor stiffness may be factors. Amplitude asymmetries have similar implications. In addition, contracture may limit extension amplitude
- Motor point block of FCU and/or ECU can help sort their contributions to ulnar deviation

#### *Findings and Treatment Options*

- Consider chemodenervation with botulinum toxin for overactive wrist flexors and finger flexors without significant contracture
- When contracture and overactivity are both important limiters of range, chemodenervation and serial casting are considered. When chemodenervation is used, some delay before cast application may be necessary to allow for chemodenervation to take hold. Alternatively, proximal median nerve infiltration with local anesthetic can block not only most of the major wrist flexors but also most of the extrinsic finger flexors. Proximal ulnar nerve block can be added, if needed
- When additional neurological recovery is not expected, consider surgical tendon lengthenings and carpal tunnel release as indicated

### **The Clenched Fist Deformity**

#### *Description, Functional Consequences and Penalties*

- S&S: fingers clenched into the palm, wrist most often flexed but some patients have an extended wrist that will exacerbate finger flexion by tenodesis: malodor and maceration are common; skin breakdown occurs when fingernails dig into the palm
- PF: washing, and maintaining a dry, clean palm, donning splints and gloves, filing and painting fingernails all pose problems for patients with a clenched fist and for their caregivers (Figure 35-14)
- AF: impaired finger extension during reaching; individual fingers or groups of fingers may be flexed; flexed index and long fingers impair object acquisition by web space on radial side of hand (Figure 35-15)



**FIGURE 35-14**

An example of passive dysfunction of the hand reflected by poor cleanliness and hygiene of the hand. A clenched fist reduces access to the palm for cleaning and leads to moisture retention, malodor, and tissue maceration

#### *Differential Diagnosis and Diagnostic Work Up*

- Muscles that may contribute: flexor digitorum sublimis (FDS), flexor digitorum profundus (FDP); intrinsic overactivity may be masked by strength of extrinsics; extensor digitorum communis (EDC) (weakness)
- Resting position: When FDP is overactive, fingernails are not easily seen as they dig into the palm; when FDS but not FDP is involved, the distal interphalangeal joint (DIP) is extended, the fingernails are visible and the proximal interphalangeal joint (PIP) is flexed
- Passive stretch: we examine with elbow relatively extended and wrist in neutral (when possible) so as not to be fighting overly tight wrist flexors; finger flexor tension is reduced by flexing the wrist and this allows assessment of intrinsic musculature (interossei and lumbricales) as well as finger joints for contracture; though many examine the group of extrinsic finger flexors as a whole, we prefer to examine FDS and FDP for each finger individually,



**FIGURE 35-15**

This photo reveals that individual fingers can be differentially involved in the clenched fist deformity. The flexed index finger and flexed thumb of this patient narrowed the web space opening on the radial side and limited the size of objects that could be acquired by the hand. Focal chemodenervation applied solely to the muscle slip of flexor digitorum of the index finger and to flexor pollicis longus is indicated

keeping in mind that FDP flexes the DIP joint while FDS flexes the PIP joint

- Dynamic EMG with wire electrodes helps distinguish behavior of FDS and FDP during voluntary tasks such as reaching. Dynamic EMG is also useful in determining intrinsic muscle behavior, especially when the stronger extrinsics dominate the clinical picture; wire electrode recordings reveal voluntary behavior of EDC
- When selective voluntary extension of the fingers falls short of the available passive range, flexor overactivity and weakness of extensor digitorum communis are likely. Contracture of finger flexors is also common
- When a patient is able to do alternating voluntary flexion and extension, timing and amplitude asymmetries can be identified. When extension movements are visibly longer in time than flexion movements, overactivity of flexors is likely, but extensor digitorum communis weakness is typical and flexor stiffness may be a factor. Amplitude asymmetries have similar implications. In addition, contracture may limit extension amplitude

#### *Findings and Treatment Options*

- Consider chemodenervation with botulinum toxin for overactive finger flexors without significant contracture.
- When contracture and muscle overactivity limit range, chemodenervation followed by aggressive ranging and serial splinting may be considered.
- FDS can be chemodenervated separately from FDP. Individual muscle slips of FDS and FDP can be identified by electrical stimulation through the injecting

hypodermic needle. We use electrical stimulation to guide chemodenervation of FDS and FDP because EMG guidance is less certain for these deep muscles.

- When additional neurological recovery is not expected, consider tendon lengthenings. A superficialis to profundus transfer is considered for a non-functional hand with major hygiene problems.

### The Thumb-in-Palm Deformity

#### *Description, Functional Consequences and Penalties*

- S&S: thumb flexed into the palm at rest or with effort (Figure 35-16); thumbnail digs into skin
- PF: impaired access to palm for washing, donning gloves; psychologically bothersome appearance
- AF: impaired 3 jaw chuck, key pinch, other types of grasp; small web space limits size of objects that can be acquired by the radial side of the hand

#### *Differential Diagnosis and Diagnostic Work Up*

- Muscles that may contribute: flexor pollicis longus, and brevis, adductor pollicis, 1st dorsal interosseous
- Thumb range, tone examined with wrist extended and flexed; thumb intrinsics examined with wrist flexed
- Flexion of distal interphalangeal joint (DIP) suggests FPL involvement; carpometacarpophalangeal joint flexion with a flexed wrist points to potential involvement of FPB; a narrowed web space and adducted thumb suggests potential involvement of AP and/or 1st DI
- Voluntary thumb extension is tested with the wrist flexed in order to minimize FPL tightness
- Ulnar nerve block in Guyon's canal eliminates overactivity in AP and 1st DI, opening the web space
- If the web space remains narrow, muscle contracture is suggested; examine for skin contracture as well



**FIGURE 35-16**

Example of a thumb-in-palm deformity. Flexor pollicis longus is clearly involved. Flexor pollicis brevis must also be considered because of flexion of the metacarpophalangeal joint

- Median nerve block in carpal tunnel eliminates median innervated intrinsics of the thenar eminence
- Dynamic EMG of thumb intrinsics and extrinsics may be useful in localizing muscle overactivity

#### *Findings and Treatment Options*

- If diagnostic block of ulnar nerve in Guyon's canal opens the web space, muscle overactivity without contracture is the likely cause of an adducted thumb
- Consider botulinum toxin for muscle overactivity without contracture
- If web space remains tight after block, muscle contracture is likely; examine for joint contracture as well
- During early recovery, stretching exercises, dynamic splinting, serial casting may be considered
- If FPL is overactive, consider botulinum toxin injection; stretch FPL contracture after toxin injection
- When further neurological recovery is not expected, skin, muscle and joint contractures may be handled surgically
- When thumb flexion is weak, fusion of the DIP joint may enhance pinch power; when thumb flexion is adequate, thumb extension by an orthosis with elastic properties is theoretically desirable but often difficult to fabricate
- Chemical or surgical relief of the thumb-in-palm (TIP) deformity can enhance 'hand as a holder' function i.e. the insertion of objects into the TIP hand for useful holding (without manipulation)

### The Flexed Hip Deformity

#### *Description, Functional Consequences And Penalties*

- Flexed hip deformity during stance phases with forward flexed trunk. (Figure 35-5)
- Other findings include compensatory knee flexion during stance phase and relative leg length discrepancy with increased energy consumption. Limited hip extension with shortening of the contralateral step length. Hyperlordosis in an attempt to keep upright posture.

#### *Differential Diagnosis and Diagnostic Work Up*

- Muscles, which can contribute to this deformity, include the iliopsoas, rectus femoris and in some cases the hip adductors and pectineus.
- Hip range of motion should be examined with the Thomas test reducing spine motion. The Eli test will help elucidate the contribution of the rectus femoris to the deformity.
- The hip flexion may be caused as a compensation for equinus deformity and will be evident only during

walking but not confirmed by passive range of motion examination of the hip. Involvement of the rectus femoris may be clinically elucidated by observation of gait with knee extension and hip flexion occurring always together.

- Dynamic EMG is helpful in clarifying the contribution of rectus femoris vs. hip adductors and iliopsoas.
- Radiographs should be obtained to rule out bony deformity of the hip.
- Obturator nerve block or a motor branch block to the rectus femoris with local anesthetic can help differentiate the role of the hip adductors vs. iliopsoas or rectus femoris vs. iliopsoas.
- Increase stance phase hip extension following a diagnostic block helps to determine contribution from other muscles.
- Persistent hip flexion post block will point to the iliopsoas as the deforming force.
- Hip adduction deformity may be present in conjunction with flexion.

#### *Findings and Treatment Options*

- If a temporary nerve or motor branch block results in increased hip extension, muscle overactivity without contracture of the hip adductors or rectus femoris is the likely cause of the deformity.
- If the hip flexion persists and no radiographic evidence of bony involvement is evident, iliopsoas is the source of the deficit.
- Botulinum toxin could then be injected into the iliacus followed by stretching. If there is no change in the hip range of motion a contracture is determined.
- In the early period of recovery, stretching and botulinum toxin to control hip flexion is considered.
- If EMG studies or blocks demonstrate static origin to the deformity or sufficient time has elapsed for further neurological recovery, surgical intervention should be considered.
- Stretching of the hip flexors and strengthening of the hip extensors should be undertaken.

#### **The Adducted Hip Deformity**

##### *Description, Functional Consequences And Penalties*

- Adducted hip deformity during swing phase with narrow base of support. (Figure 35-17)
- Other findings may include associated hip flexion and relative leg length discrepancy with decrease stability in stance phase. Limited hip extension with shortening of the contralateral step length and difficulty with limb advancement in swing phase.



**FIGURE 35-17**

The consequence of an adducted hip is a narrow base of support

#### **DIFFERENTIAL DIAGNOSIS AND DIAGNOSTIC WORK UP**

- Muscles, which can contribute to this deformity, include the adductor magnus, adductor brevis and adductor longus, in some cases the iliopsoas and pectineus may be involved.
- Hip range of motion with hips in flexion and extension should be examined.
- Limitation in hip extension may be secondary to the limitation in hip abduction.
- Dynamic EMG is helpful in clarifying the contribution of the adductor magnus, adductor brevis and adductor longus and the lack of activation of the gluteus medius.
- Radiographs should be obtained to rule out bony deformity of the hip.
- Diagnostic Obturator nerve block with local anesthetic can help differentiate muscle overactivity from contracture.



- Increase hip abduction with widening of the base of support following a diagnostic block helps to differentiate muscle overactivity from contracture.
- Persistent hip flexion post block will point to the pectineus or iliopsoas as deforming forces.
- Hip flexion deformity may be present in conjunction with adduction.

#### *Findings and Treatment Options*

- If a temporary nerve block results in increased hip abduction, spasticity without contracture of the hip adductors is the likely cause of the deformity.
- If the hip adduction persists and no radiographic evidence of bony involvement is evident a contracture is the likely source of the deformity.
- Phenol or botulinum toxin can be used to achieve longer term relief of over-activity in the early period of recovery, stretching of the hip adductors and strengthening of the abductors should follow these interventions.
- If over-activity is severe, obturator neurectomy can be entertained.
- If blocks demonstrate a static origin of the deformity or neurological recovery has lapsed, hip adductor tenotomy should be considered.
- Stretching of the hip flexors and strengthening of the hip extensors should be undertaken.

### **The Stiff Knee Deformity**

#### *Description, Functional Consequences And Penalties*

- Stiff knee deformity during swing phase with impairment of limb clearance. (Figure 35-3)
- Limited limb advancement in swing phase.
- Other findings include pelvic hick and trunk lean during stance phase and relative leg length discrepancy with increased energy consumption. Ipsilateral circumduction and contralateral vaulting as compensatory mechanisms in swing phase.

#### *Differential Diagnosis and Diagnostic Work Up*

- Muscles, which can contribute to this deformity, include the quadriceps, hamstrings, iliopsoas and gastrocnemius.
- Knee range of motion should be examined with the hip extended and flexed.
- The knee extension caused by the quadriceps is often noted by inspection during ambulation. Hip extension reduces the stiff knee deformity.
- Dynamic EMG is helpful in differentiating the contribution of muscles such as the vastii from the rectus femoris.

- Radiographs should be obtained to rule out bony deformity at the knee or hip.
- Femoral nerve motor branch block in the anterior thigh with local anesthetic can help differentiate the role of overactive knee extensors vs. hip extensors.
- Increase swing phase knee flexion following a diagnostic block helps to determine ambulatory potential.
- Persistent knee extension post femoral motor branch block will point to the hip extensors or ankle plantarflexors as the deforming force.
- Ankle plantarflexion deformity may be present in conjunction with stiff knee.

#### *Findings and Treatment Options*

- If a temporary diagnostic femoral nerve motor branch block results in increased knee flexion, spasticity without contracture is the likely cause of the deformity.
- If the knee extension persists hip extensors may be the cause of the deformity.
- If EMG studies or blocks demonstrate dynamic origin to the deformity, botulinum toxin injection or motor branch block with phenol should be considered.
- Botulinum toxin injection of the hip extensors should be considered.
- Stretching of the knee extensors and strengthening of the knee flexors should be undertaken.
- Surgery in the form of a transfer of the rectus to the gracilis and lengthening of the vastii is considered in late recovery.

### **The Flexed Knee Deformity**

#### *Description, Functional Consequences And Penalties*

- Flexed knee deformity during stance phase with knee instability with weight bearing. (Figure 35-2)
- Limited knee extension in the terminal swing phase
- Other findings include pelvic drop and trunk lean during stance phase and relative leg length discrepancy with increased energy consumption. Limited knee extension with shortening of the step length.

#### *Differential Diagnosis and Diagnostic Work Up*

- Muscles, which can contribute to this deformity, include the hamstrings, gracilis, gastrocnemius and adductor longus.
- Knee range of motion should be examined with the hip extended and flexed.
- The knee flexion caused by the hamstrings is often noted by inspection during ambulation. Hip extension reduces the flexed attitude of the knee.
- Dynamic EMG is helpful in clarifying the contribution of muscles such as the medial vs. lateral hamstrings or the adductor longus.

- Radiographs should be obtained to rule out bony deformity at the knee.
- Sciatic nerve motor branch block in the gluteal fold with local anesthetic can help differentiate the role of dynamic spasticity with respect to contracture in this deformity.
- Increase stance and swing phase knee extension following a diagnostic block helps to determine ambulatory potential.
- Persistent knee flexion post sciatic nerve block will point to the hip adductors as the deforming force.
- Hip adduction deformity may be present in conjunction with flexion.

#### *Findings and Treatment Options*

- If a temporary diagnostic sciatic nerve motor branch block results in increased knee extension, spasticity without contracture is the likely cause of the deformity.
- If the knee flexion persists hip adduction may be the cause of the deficit.
- If there is no significant change in the knee range of motion after a sciatic nerve block, a static deformity i.e., knee contracture is determined.
- In the early period of recovery, orthotic management to control knee flexion is considered.
- If EMG studies or blocks demonstrate dynamic origin to the deformity, Botulinum toxin injection or motor branch block with phenol should be considered.
- Stretching of the knee flexors and strengthening of the knee extensors should be undertaken.
- Surgery in the form of distal hamstrings lengthening is considered for a static deformity in late recovery.
- A capsular release is considered if knee flexion is present while under general anesthesia.

#### **The Equinovarus Foot Deformity**

##### *Description, Functional Consequences and Penalties*

- Abnormal base of support during stance phase with weight bearing applied to the lateral border of the foot with pain and ankle instability with antalgic gait pattern.
- Equinovarus posturing in swing phase
- Other findings include hyperextension at the knee with recurvatum thrust (Figure 35-18), impaired forward progression of the center of gravity and relative leg length discrepancy with increased energy consumption.

##### *Differential Diagnosis and Diagnostic Work Up*

- Muscles, which can contribute to this deformity, include the gastrocnemius, soleus, tibialis anterior,



**FIGURE 35-18**

This patient has plantarflexor overactivity and contracture leading to hyperextension at the knee with recurvatum thrust and impaired forward progression of the body over the stance phase limb

tibialis posterior, extensor hallucis longus, extensor digitorum, flexor digitorum and foot intrinsics (Figure 35-19).

- Ankle range of motion should be examined with the knee extended and flexed.
- The inversion pull of tibialis anterior is often noted by inspection during ambulation. Hind foot inversion is often generated by spastic tibialis posterior.
- Dynamic EMG is helpful in clarifying the contribution of muscles such as the tibialis posterior and anterior.
- Radiographs should be obtained to rule out bony deformity at the ankle.
- Tibial nerve block in the popliteal fossa with local anesthetic can help differentiate the role of dynamic spasticity with respect to contracture in this deformity.
- An improved base of support following a diagnostic block helps to determine ambulatory potential.
- Persistent ankle inversion post tibial nerve block will point to the tibialis anterior as the deforming force.
- Curled toes may be associated with the equinovarus deformity and worsened by increase ankle dorsiflexion.



**FIGURE 35-19**

Two feet with equinovarus deformities in the same patient. As confirmed electromyographically, left foot varus was attributable to tibialis anterior overactivity. Right foot varus was driven by tibialis posterior overactivity. Note bilateral great toe hyperextension, variously termed: striatal toe or hitchhiker's toe

#### *Findings and Treatment Options*

- If a temporary diagnostic tibial nerve block results in increased ankle dorsiflexion, spasticity without contracture is the likely cause of the deformity.
- If varus persists in swing phase, the most likely cause is tibialis anterior and/or extensor hallucis longus.
- If there is no significant change in the range of motion after a tibial nerve block, a static deformity i.e., contracture is determined.
- In the early period of recovery, orthotic management to control equinus is considered, with appropriate components to control ankle inversion and toe flexion.
- If EMG studies or blocks demonstrate dynamic origin to the deformity, Botulinum toxin injection or percutaneous motor point blocks with phenol should be considered.
- Stretching of the ankle plantar flexors and strengthening of the ankle dorsiflexors should be undertaken.
- Surgery in the form of tendo Achilles lengthening or intramuscular lengthening is considered for a static deformity in late recovery.
- A SPLATT (Split Anterior Tibialis Tendon Transfer) is considered if ankle inversion is present during swing phase and is caused by tibialis anterior. If inversion is caused preferentially by tibialis posterior, a lengthening of this muscle is indicated.

#### **Concepts in Pharmacological Intervention**

Pharmacological reduction of muscle overactivity may be beneficial in selected clinical problems. However, drug

treatment of overactivity is often a trade off against side effects. Three drugs, dantrolene sodium, baclofen and diazepam are commonly used to treat spasticity. Their use in TBI must be considered carefully because the side effect of sedation, though typically different for each drug, can be problematic for patients with arousal or cognitive dysfunction. It is ironic and sobering that patients with TBI, who often need help for muscle overactivity more than most, are also among the most sensitive to the side effects of these agents with respect to functions such as attention and cognition.

*Dantrolene Sodium* Dantrolene sodium exerts its effect directly on skeletal muscle fibers. Physiologically, a neural signal to a muscle triggers a motor unit action potential that causes release of calcium from sarcoplasm storage sites within the muscle fiber itself. Calcium ions initiate cross-bridging of myofilaments and build-up of contractile tension. By inhibiting release of calcium from the sarcoplasmic reticulum, dantrolene sodium reduces the force of muscle contraction and, thereby, has the potential for reducing tension in overactive muscles. It should be noted that tendon jerk responses and electrically induced twitch tensions of muscle are reduced much more effectively than tetanic stimulation or sustained volitional contraction. In the latter conditions, the amount of calcium released into the sarcoplasmic reticulum over the course of continued stimulation of muscle by nerve activity (whether through volition or through electrical stimulation) tends to accumulate and overcome the inhibitory effects of the drug. This latter observation is important in understanding the utility and limitations of dantrolene sodium as a clinical agent. Dantrolene sodium may be useful in treating short duration, low frequency spastic phenomena such as clonus or brief spasms (49) (Figure 35-4). Phasic, small tension overactivity rather than tonic, large tension overactivity is favored for treatment with dantrolene sodium. Patients with TBI who have severe overactivity are not typically responsive to dantrolene sodium. Though its influence on treating spasticity is peripheral, dantrolene sodium apparently has a number of side effects that are central in nature and it can be sedating to patients with arousal dysfunction. Nevertheless, it may be a reasonable choice for mild to moderate overactivity, especially for clonus or other phasic behaviors involving many different muscles. Clonus often remits at a dose level of 50 mg q.i.d. though doses of up to 400 mg a day may be used. Cases of hepatotoxicity have been reported and liver function tests should be monitored, especially in those at risk for liver toxicity for other reasons.

*Diazepam* This agent, centrally acting and highly sedating, increases the central inhibitory effects of gamma amino-butyric acid (GABA) (50). Diazepam appears to bind to receptors located at GABA-ergic synapses and

increases GABA-induced inhibition at those sites. Antispastic characteristics of diazepam appear to arise from GABA-related inhibitory effects on alpha motor neuron activity in the spinal cord. Since diazepam also exerts sedative effects in the brain, some of its muscle relaxant properties may be due to diazepam's ability to produce a more generalized state of sedation. Although it is often successful in reducing spasticity of skeletal muscle, the primary problem with diazepam is sedation. Diazepam is not a suitable drug for persons with TBI who have attention or cognitive dysfunction. For patients who have persistent phasic flexor spasms that disturb activities of daily living or nighttime sleep, small doses of diazepam may be effective in reducing the frequency and intensity of these spasms with tolerable sedation.

**Baclofen** This drug, a derivative of GABA, appears to act as a GABA agonist inhibiting transmission at specific synapses within the spinal cord (51). When used as an antispastic agent, baclofen ultimately appears to have an inhibitory effect on alpha motor neuron activity. It is unclear whether this inhibition is presynaptic (through inhibition of other excitatory neurons that synapse with the alpha motor neuron), or whether it is postsynaptic on the alpha motor neuron itself. Nevertheless, the net result of baclofen's action is to inhibit the firing pattern of the alpha motor neuron pool in the spinal cord with subsequent reduction of muscle overactivity in skeletal muscles.

Clinical research studies using baclofen for overactivity have primarily addressed the problems of patients with multiple sclerosis or spinal cord injury (52). Baclofen has been effective in these populations, especially when the clinical problem has related to flexor spasms. Oral baclofen is generally initiated at 10 mg a day in divided doses and increased to 80 mg or more as needed. Such high doses will invariably lead to side effects in many patients that can overshadow any benefits. In patients with TBI who are in a persistent vegetative state and are not expected to recover, high doses may be considered since cognitive and arousal function are not an issue. Nevertheless, on the remote possibility that the patient might be making some recovery, it might be wise to taper the drug periodically and observe.

Oral baclofen has been little studied in spasticity of cerebral origin (53). Meythaler et al. performed a retrospective review of 35 adult patients with acquired brain injury before and after starting treatment with oral baclofen. Twenty two patients had TBI and were found to have a change in Ashworth grade and deep tendon reflexes in the lower limbs. For the upper limbs, no significant change in Ashworth grade or deep tendon reflexes and spasm frequency didn't change in upper or lower limbs. The average dosage at follow-up was 57 mg baclofen (range: 15–120 mg/day). For the group as a whole, a 17% incidence of somnolence limited the maximum daily

dosage. The authors speculated that the lack of effect of oral baclofen on Ashworth scores and tendon reflexes may have been related to their observation that systemic delivery may have profound central side effects at brain level before it reaches adequate concentrations at cervical cord level necessary for affecting upper limb spasticity. Drowsiness, confusion and memory impairment are known side effects of oral baclofen and can be particularly troublesome for patients with TBI who already have impairments of arousal, attention and cognition (52, 54). A potential method for reducing central side effects is the intrathecal delivery of baclofen (ITB)(55), an approach for controlling hypertonia in ABI that has more extensive literature than oral ingestion. A drug pump is implanted subcutaneously to infuse baclofen into the lumbar subarachnoid space. Compared with oral administration, the pump allows much smaller doses of baclofen to be used (56–58). Side effects are reduced and effectiveness in refractory cases is enhanced (53). The pump has an eighteen milliliter reservoir, connected to an intrathecal catheter, that is refilled periodically by percutaneous puncture. The rate of baclofen infusion is adjusted by an external computer. The most common adverse effects of ITB include hypotonia, drowsiness, dizziness, nausea, vomiting, hypotension and headache (59, 60). Life-threatening complications associated with overdose or withdrawal have occurred, linked to mechanical failure or human error. (61–64) Intrathecal overdose can cause coma and respiratory depression. Sudden withdrawal of the drug (e.g. by unrecognized pump failure) can cause an exaggeration of spasticity along with hallucinations and seizures. The system is expensive and potentially hazardous when technical problems arise. However, the pump system may be useful for patients who have regional muscle over-activity distributed across many lower extremity muscle groups, especially bilateral hip flexor, adductor and hamstrings groups. Most studies with ITB (as with oral baclofen) have focused on the evaluation of stretch reflexes and spasms and active function has not been systematically investigated (53, 65). In a pilot study, Francisco and Boake reported an improvement in walking speed in 10 patients with poststroke spastic hemiplegia after ITB in combination with physical therapy.

**Tizanidine** Tizanidine has muscle relaxant properties, acting as an agonist at alpha-2 adrenergic receptor sites both spinally and supraspinally. Placebo-controlled studies have shown that tizanidine reduces muscle response to passive stretch in both the spinal and cerebral forms of spasticity including patients with TBI (66–68). Tizanidine does not appear to confer functional changes (67, 69). Adverse effects have included hypotension, sedation, generalized fatigue, falls, dry mouth, reduced renal clearance and the potential for hepatotoxicity and

hypotension (70). Sedation, a particular problem for patients with TBI, is the commonest adverse effect, occurring in almost 50% of patients who use it (71). The amount of tizanidine that a clinician can use for patients with TBI is necessarily curtailed by its side effects, particularly drowsiness. Hence, its therapeutic effect for muscle overactivity is often limited. In addition to spastic stretch reflexes, tizanidine has been shown to have a physiologic effect on co-contraction, a common positive sign of UMN activity that hampers voluntary movement (29).

### Botulinum Neurotoxin (BoNT)

Pharmacological management of muscle over-activity often requires a balance between acceptable reduction in over-activity and acceptable side effects. From this perspective, botulinum neurotoxin (BoNT) is an excellent therapeutic agent because of its focal action without significant side effects. A number of double-blind, placebo-controlled studies have reported significant reductions in muscle tone for patients with acquired brain injury, primarily stroke (72–74). Yablon et al. performed an open-label study of 21 patients with TBI who had severe wrist and finger flexor spasticity (75). Improvements were seen in range of motion at the wrist and in the modified Ashworth scale. There were no significant side effects. Brashear, Gordon, Elovic et al. performed a large scale multi-center trial that was a randomized, double-blind, placebo-controlled study of BoNT A in persons with spasticity of the wrist and finger flexors after a stroke (76). The study assessed efficacy and safety of BoNT A in 126 subjects who received a one-time injection of 200 to 240 units. The primary outcome measure was self-reported disability in four areas: personal hygiene, dressing, pain and limb position at six weeks. At base line, each subject selected one of these areas as the principal target of treatment. Based on Ashworth scores, they found significantly greater improvement in subjects treated with BoNT A in wrist and finger flexor tone at all follow-up visits through 12 weeks than did subjects who received placebo. In addition, subjects treated with BoNT A had greater improvement in the principal target of treatment at weeks 4, 6, 8 and 12. There were no major adverse events associated with injection of the neurotoxin. Brashear, Zafonte, Corcoran et al. demonstrated inter- and intrarater reliability for the the Disability Assessment Scale as well as for the Ashworth Scale applied to elbow, wrist, finger and thumb flexors of poststroke patients (77). Brashear et al. have reported results of an open-label, single-treatment session using BoNT B (MyoBloc; Elan) in 10 patients with upper limb spasticity (elbow, wrist, fingers) (78). Improvements in Ashworth scores as well as global assessment changes by investigators and patients were obtained. Nine of 10 subjects reported dry mouth at week 4 of the study with resolution by week 12. No changes were seen on functional measures.

BoNT type A (BoNT A) is injected directly into affected muscle groups, usually under electromyographic or electrical stimulation guidance, causing reversible, dose-dependent muscle relaxation by blocking acetylcholine release at the neuromuscular junction (Figures 35-20 and 35-21). The purpose of toxin injection is to reduce force generated by UMN muscle over-activity in order to create a more favorable net balance of forces acting across joints (Figures 35-22 and 35-23). When target muscles are identified, the toxin's localized inhibitory effect makes it a very useful agent for carrying out focal strategies for managing muscle over-activity. A reduction in excessive tension can lead to improvement in passive and active range of motion and allows for more successful stretching of dynamically and statically tight musculature. More subtly, and more importantly, a patient's improved control over movement and posture may allow for compensatory behaviors during functional activities that rely on active as opposed to passive movement. A reduction in muscle over-activity in one muscle group may have consequences for tone in other muscle groups of the limb through a reduction in the overall effort required to perform movement and/or possibly through changes in sensory information going to the central nervous system from that limb.

In contrast to phenol or alcohol, exposure to the toxin causes reversible denervation atrophy without fibrosis. There are seven serologically distinct toxins produced by *Clostridium botulinum* that are potent

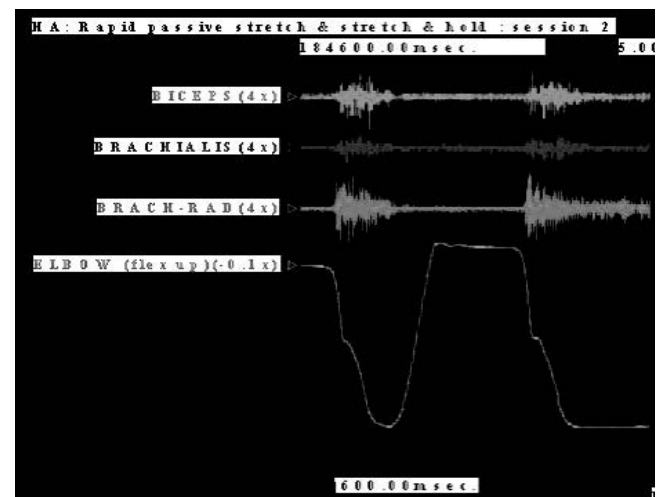


FIGURE 35-20

Prior to injection of BoNT A: Rapid passive stretch of elbow flexors followed by rapid passive stretch and hold in a patient with TBI and hemiparesis reveals spastic reactivity in all three elbow flexors during dynamic stretch. Tonic activity is also seen in brachioradialis during static stretch (“hold” phase). Bottom movement trace shows a “spastic catch” midway during displacement

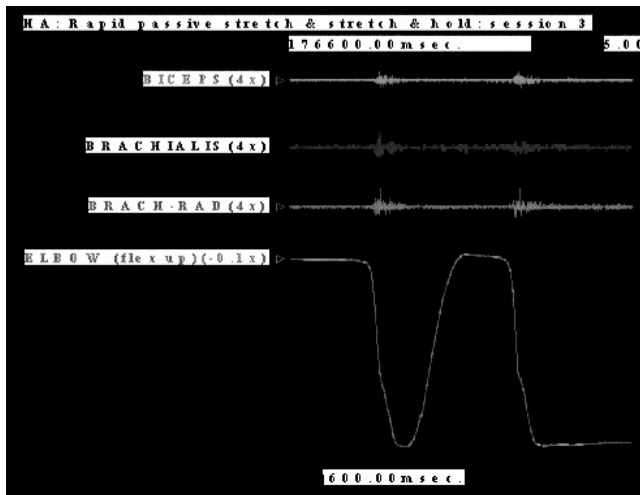


FIGURE 35-21

Biceps was injected with 120 units BoNT A (Botox®); brachioradialis was injected with 80 units. The figure is a 22-day follow-up study: Note marked reduction in stretch reflex activity and absence of “spastic catch” in the movement trace, as reflected in EMG of all flexors during stretch. BoNT A inhibits muscle contraction by blocking acetylcholine release at the neuromuscular junction

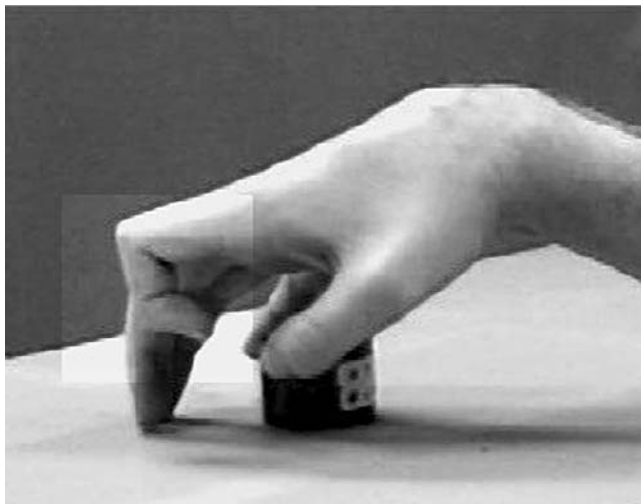


FIGURE 35-22

Flexed index finger during reach to grasp in a 22-year-old woman two years after TBI. Muscle overactivity on the radial side of the hand impairs access of objects into the webspace of the hand

neuroparalytic agents and these are designated as BoNT A, B, C, D, E, F and G. Only two types (A and B) are available for therapeutic human use. BoNT type A is synthesized as single chain polypeptides with a molecular mass of approximately 150 kDa. Neurotoxin activation



FIGURE 35-23

Twenty-two days after injection of 20 units BoNT A (Botox®) into isolated muscle fascicles of flexor digitorum profundus and flexor digitorum sublimis of the index finger. Access to the webspace was improved and objects were more easily grasped

requires a two-step modification in the structure of the protein. In the first step, the parent chain is cleaved. The result is the formation of a heavy chain tethered by a disulfide bond to a light chain that is associated with one atom of zinc. The second activation step, disulfide reduction requires internalization by the target cell. The toxin must enter the endplate zone to exert its effect. The process is partially dependent on nerve stimulation and independent of  $Ca^{2+}$  concentration. A commercial form of BoNT A in the United States (US) is Botox® [Allergan] which is currently approved by the US Food & Drug Administration (FDA) for the treatment of blepharospasm, facial spasm, strabismus, cervical dystonia and torticollis and certain cosmetic uses. BoNT B is branded as MyoBloc [Solstice] and is approved for the treatment of cervical dystonia in the US. Dysport is a different (non-interchangeable) version of BoNT A that is available in Europe and elsewhere but not the US. In Europe and Canada, BoNT A is also approved for the management of spasticity secondary to cerebral palsy and stroke.

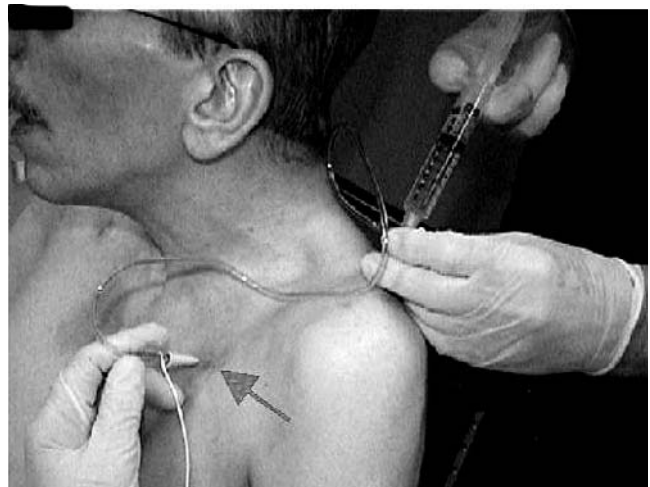
Patients may begin to experience benefits three to seven days after injection. The duration of action in the management of muscle overactivity is about three to four months, after which re-injection is indicated. Reported adverse effects have included excessive weakness of injected muscles, pain at injection site, local irritation, headache, fatigue and flu-like symptoms. No anaphylactic response has ever been reported due to BoNT A injection. Treatment success, in part, depends on the skill of the injector. Muscle selection, injection technique and dose must be individualized. (see Table 35-1)

**Nerve Blocks** Nerve and motor point blocks are very useful in targeting specific muscles or muscle groups for diagnostic and therapeutic maneuvers. The purpose of the nerve or motor point block is to reduce force produced by a contracting spastic muscle or muscle group. A reduction in spastic tension can lead to improvement in passive and active range of motion and allows for more successful stretching of tight musculature. More subtly, and more importantly too, a patient's improved control over movement and posture may allow for compensatory behaviors during functional activities. A reduction in spastic activity in one muscle or muscle group may have consequences for tone in other muscle groups of the limb through a reduction in the overall effort required to perform movement and/or through changes in sensory information going to the central nervous system from that limb. Finally, the application of external devices such as braces, casts, even shoes, can be facilitated by nerve and motor point blocks.

Blocks may be classified broadly as diagnostic or therapeutic in nature. Diagnostic blocks are typically performed with short acting local anesthetics such as lidocaine or bupivacaine. These quick acting, short duration agents allow the examiner to evaluate factors described above such as passive range of motion, muscle stiffness unrelated to overactivity, changes in active range of motion when dynamic resistance is blocked, and enhanced motor control during functional movements. For example, a patient with overactive adductors causing scissoring during gait may be prone to fall because of the narrow base of support. A temporary block of the obturator nerve with 2% lidocaine will allow the examiner to observe whether the base of support widens and stability improves. The key to understanding the use of a diagnostic nerve block is that it be used to test a hypothesis. In the given example, the hypothesis behind the obturator nerve block is that the base of support was narrowed by excessive adduction of the leg caused by spastic adductors. It was further postulated that a wider base of support would lead to greater stability during dynamic gait. After the nerve block is performed with a quick-acting local anesthetic, the patient is ambulated in order to test the hypotheses about widening the base of support and improving stability during ambulation. If improved ambulation results, then more permanent (i.e. less reversible) types of intervention may be contemplated with a greater sense of outcome prediction. Therefore, the prediction of a likely outcome for an intervention is an important feature of temporary nerve or motor point blocks. In the given example, it is possible that the base of support might not widen. For example, a severe adductor contracture will not remit after a nerve block. However, this information is useful in designing the next step in the treatment program. Similarly, it is possible that the nerve block may be physiologically successful, spasticity

of the adductors are blocked, and the base of support widens. Yet the overall gait pattern is only partially improved because instability was coming from other sources of neuromuscular neurological impairment. Again, this kind of information can lead to further diagnostic testing of other hypotheses relevant to why the patient has an ambulation dysfunction.

Therapeutic nerve and motor point blocks are primarily performed with aqueous solutions of phenol. When it is injected in or near a nerve bundle, phenol denatures protein in the myelin sheath or cell membrane of axons with which it makes contact. When administered in the operating room under direct nerve visualization, phenol is instilled directly into the nerve bundle in a glycerin solution to minimize leakage. Related to this technique, the desired motor nerves are identified by electrical stimulation prior to injection, mixed nerves with sensory and motor fibers are avoided because of consequent dysesthesias, and the duration of effect is often six months or more because the injection of the nerve is so direct. An aqueous solution of phenol, on the other hand, is the medium used for percutaneous injection in the laboratory or at the bedside and the location of the nerve is approximated by an electrical stimulation technique which typically results in variable contact of phenol with axons (Figure 35-24). This variability is a key factor in the duration of effectiveness of a percutaneous phenol nerve or motor point block. As Glenn has indicated, a peripheral



**FIGURE 35-24**

Phenol injection into a motor point of pectoralis major. A motor point is defined electrophysiologically rather than by anatomy. It is the most distal location of a motor nerve at which electrical current produces a visible or palpable contraction of muscle. The hypodermic needle in the photo is insulated on the outside and has a conductive core on the inside. When connected to an electrical stimulator, the needle is used to find a motor point and, when found, to inject phenol into the region of the motor point

nerve block is more likely to last longer than a block of a motor point [a motor nerve branch located much closer to a muscle than the more proximal peripheral nerve]. Phenol neurolysis of peripheral nerve may result in Wallerian degeneration. Re-innervation probably takes longer for the proximally blocked peripheral nerve because it has a longer distance for axoplasm to advance in order to reach muscle compared with the re-innervation distance of nerve blocked at the more distal motor point. The smaller size of the nerve involved in a motor point block may also make it harder to localize percutaneously. In addition, if a mixed sensory-motor nerve is selected for phenolization [typically in a low level patient where there is less concern about consequent dysesthesia], a reduction in afferent drive of spasticity may add to the effectiveness of the block as well. It is our impression that a motor point block with phenol can influence over-activity for three to five months. Nevertheless, reports on duration effectiveness in the literature have varied over a vary broad range from several days to three years. The reader should glean from this that phenol blocks are a temporizing measure and are most effectively used in the period of expectant neurological recovery. The rationale for the other injectable agents such as alcohol and botulinum toxin, is in our view, essentially the same.

The strategy of performing a block is as follows: a surface stimulator is used to locate the selected peripheral nerve or motor point. The skin is then prepared with an antiseptic iodine solution, swabbed with alcohol and subcutaneously anesthetized with lidocaine prior to insertion of the teflon coated, 22 gauge injecting needle (see Figure 35-24). The electrically conductive inner core of the tip of the needle is used to pass current to the tissues. As the needle is advanced closer to the nerve, less current is required to produce similar amounts of muscle contraction. When a minimal current producing a visible or palpable muscle contraction is reached, we typically inject 3–5cc of aqueous phenol in concentration of 7%. When injecting multiple nerves or motor points, we usually do not exceed a total volume of 15cc and we generally avoid injecting patients taking anticoagulants where the risk of systemic absorption of phenol is greater. [In very large quantities, systemically absorbed phenol can cause seizures, central nervous system depression and cardiovascular collapse]. The essence of the technique is in the clinical manipulation of needle advancement towards the nerve. Depth of penetration and directional orientation of the needle tip require a steady hand, competent knowledge of anatomy and a good assistant. Morbidity is typically benign. Local irritation at the site of the block is treated symptomatically with ice, compression or mild analgesics. We avoid mixed sensory-motor nerves so as not to induce painful dysesthesias and we will substitute motor point blocks that involve motor branches only. The injection technique is a good temporizing measure during

the period of expectant neurological recovery and facilitates serial casting, range of motion exercises, passive ADL functions and active movements and function as well.

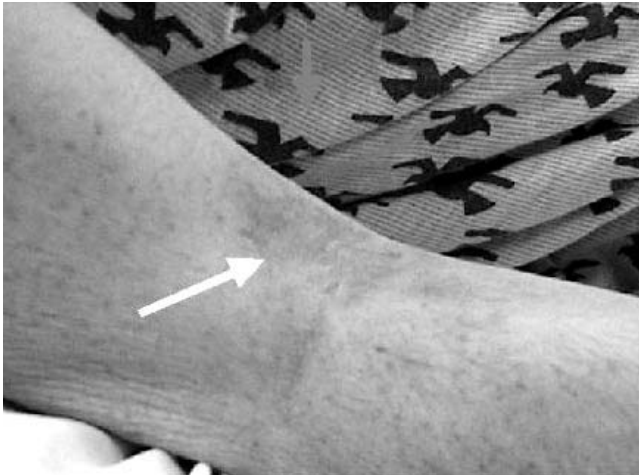
Borg-Stein et al. have made an initial comparison of phenol and botulinum toxin injections (79). They indicated that a reduction in over-activity after phenol motor point block tends to diminish after several months, but may last as long as several years. The effect of botulinum toxin appears to last for about three to four months with a more complete return to baseline than is generally seen after phenol injection. Botulinum toxin is not associated with dysesthesia, but neither is motor point block with phenol. Only injection of phenol into a mixed sensory/motor nerve may produce such an effect. The cost of the toxin compared with the cost of phenol is large and the cost will escalate if multiple injections are required to titrate a desired clinical effect. Second, it is not clear how to control the titration process for an overactive muscle that also has volitional capacity. An ideal agent would eliminate a muscle's over-activity while preserving its voluntary capacity. Third, the technique for injecting deeper muscles with toxin requires electrical stimulation to verify the muscle's identity. This requires searching skill akin to the skill of advancing toward a motor nerve using the phenol technique. For deep muscles, EMG guidance does not really specify which muscle is being injected. Such a technique may be useful in dystonia, but is riskier in UMN muscle over-activity. Phenol has local anesthetic properties so that one can see an immediate result after injection (Figures 35-25 and 35-26). Botulinum toxin effects are variably seen after 5–14 days. On the whole, injecting botulinum toxin into a single superficial muscle under EMG guidance is quicker than injecting



**FIGURE 35-25**

Phenol has local anesthetic properties so that one can see an immediate result after injection. In this photo, a prominent biceps tendon is observed when the biceps is stretched





**FIGURE 35-26**

This photo was taken 5 minutes after phenol block of the musculocutaneous nerve was performed with 4 cc of 7% aqueous phenol. The biceps tendon is no longer prominent because the local anesthetic effect of phenol has eliminated stretch reflex activity in the biceps (and brachialis). Beginnings of the longer-term denaturation effect of phenol is not expected for 48-72 hours after phenol injection

phenol but more individual muscles are injected with the toxin so that total work time may turn out to be a wash. To inject phenol, we typically utilize an assistant. Botulinum toxin can be managed entirely by the physician. Finally, BoNT and phenol can be used together in situations where large proximal muscles receive phenol blocks and smaller distal muscles receive toxin. Since the current upper range of toxin use is 600 units, large muscles would absorb most if not all of the prescribed toxin leaving little left over for many smaller distal muscles. Hence, phenol applied to proximal musculature spares toxin for use elsewhere.

### **Special Section on Neuro-Orthopaedic Principles, Selected Procedures and Post-Operative Rehabilitation for UMN Muscle Overactivity After TBI**

*Neuro-orthopaedic Principles and Perspective* Six or more months after TBI, when the patient is neurologically stable and a majority of motor recovery has occurred, decisions can be made regarding neuro-orthopaedic surgery to correct limb deformities and rebalance muscle forces. It is at this time that a neuro-orthopaedic surgeon can make the greatest contribution to a patient's functional recovery. When evaluating patients with brain injury, questions commonly arise regarding indications for surgery, cost, expected outcome, and practicality of this approach. These issues should be considered on an individual basis for each patient. We have delineated

general principles that serve as our guidelines for decision making.

*Operate Early — Before Deformities Are Severe and Fixed* Orthopaedic surgery is a powerful rehabilitation tool. It is often the only treatment that will correct a limb deformity or improve function. Surgery should not be considered a treatment of last resort when “conservative” measures have failed. The choice of treatment technique, surgical or non-surgical, should be predicated on which one will provide the most optimal result.

*Better Underlying Motor Control Means Better Function for the Extremity* Orthopaedic surgery cannot impart control to a muscle. Lengthening a spastic muscle can improve its function by improving joint range of motion, by diminishing unwanted force generated by muscle overactivity, unmasking volitional strength of agonists when antagonists are modified by lengthening and uncovering any latent motor control that was present. Successful surgery depends on a careful evaluation preoperatively to determine the amount of volitional control present in each individual muscle that is affecting limb posture and movement.

*Distinguish Between the Function of the Extremity and the Function of the Individual* We think of active function and passive function of the extremity. These terms refer to the expected outcomes for a limb but do not indicate the outcome for the person as a whole. Surgical releases of an arm contractured in a flexed and internally rotated position in a hemiplegic patient often allows the person to become independent in dressing even though the arm itself does not have volitional movement.

*Consider the Cost of Not Correcting Limb Deformities* Allowing limb deformities to occur or persist is detrimental to well being and quality of life of the person with brain injury. Likewise, the cost of laboratory based motor control evaluation using dynamic electromyography (EMG); video and motion analysis is relatively modest for the benefits it provides. Dynamic EMG is a one-time expense. The cost of performing an incorrect surgical procedure that fails to correct or worsens a limb deformity is much greater. The cost of performing a surgical procedure is likewise limited when compared to a lifetime of attendant care, spasticity medications, repeated blocks, orthotics to control limb position, complications such as skin ulceration and infection and lost productivity for the patient and caregivers.

*Perspective on Neuro-Orthopaedic Treatment of Muscle Overactivity* Treatment of muscle overactivity is most effective when functional problems are formulated in focal rather than diffuse terms. For example, a patient may have muscle overactivity across all joints of the upper

extremity that some might consider sufficient justification for the use of a systemic agent to reduce tone in the arm as a whole. A closer examination of the patient might reveal that function of one joint in particular is most important. Treatment of focal problems lends itself well to surgical intervention that can target particular muscles. Surgical lengthening, transfer or release of targeted muscles can provide very effective solutions to problems of function that are clearly identified from the outset. The localizing approach is useful because it forces the clinician to indicate the desired outcome in advance since the outcome is based on an analysis that identifies the specific muscles responsible for the problem. For example, if the clinical problem is an adducted shoulder that hinders access to the axilla for purposes of bathing and hygiene, blocking the pectoralis major or surgically releasing it will not solve the problem if the teres major and latissimus dorsi are really the culprits responsible for the problem. Identifying the specific offending muscles by using the technique of dynamic electromyography is critically important to localized strategies of intervention.

In a neurologically impaired patient, it is frequently difficult to distinguish between the many potential causes of limited joint motion. The possibilities include increased muscle tone, myostatic contracture, the presence of peri-articular heterotopic ossification (HO), an undetected fracture or dislocation, joint subluxation, pain, or the lack of patient cooperation secondary to diminished cognition. Bony deformities may not exhibit an obvious clinical deformity but can be detected by radiography. Various muscles may contribute to motor dysfunction across joints and limb segments in these clinical patterns. Evaluation focuses on the following characteristics of the involved joint and limb segment: (1) the extent of voluntary or selective control, particularly within the context of whole limb movements; (2) the nature and intensity of muscle overactivity; (3) the degree of rheologic stiffness; and (4) the severity of contracture. When many muscles cross a joint, the characteristics of each muscle may also vary. Because each muscle may contribute to motion and movement of the joint, information about each muscle's contribution is useful to the assessment as a whole. Treatment depends on information that is obtained from a variety of sources including a history of signs and symptoms, a history of passive and active dysfunction with everyday usage, clinical examination, radiography, multi-channel dynamic EMG studies, kinetic and kinematic measurements, videography and photography, temporary nerve blocks, casting and splinting and even empirical trials with longer term blocking agents.

### **Technique and Post-Operative Rehabilitation of the Shoulder**

*General Comments* Shoulder problems are most often the result of a combination of both neurogenic and

mechanical factors. The mechanical problems include fracture malunions, joint subluxation, adhesive capsulitis, heterotopic ossification (HO), and soft tissue contractures. Together these cause the static component of the deformity. The dynamic component of the deformity or dysfunction is the result of neurogenic factors such as weakness, impaired motor control and the various forms of muscle overactivity. Extremity impairments are also classified as to whether they are symptomatic, cause problems of active function or passive function. Active function implies that the person has some capacity or potential to move the extremity volitionally. The shoulder places the hand in space, enabling a person to access and control tasks performed in a large sector of three-dimensional space. Problems of active shoulder function are characterized by impaired reaching, pushing, pulling, wiping, stabilizing and many other actions that depend on proximal strength, dexterity and control. Passive function indicates that little or no active movement of the extremity is possible. Problems of passive shoulder function in an immobile extremity include pain, skin maceration, malodor, ulceration, and contractures that impair passive mobility needed for hygiene, dressing and comfortable positioning.

*Anterior Shoulder Release for Contracture* An incision is made on the anterior shoulder beginning at the coracoid process and extending distally. The tendinous insertion of the pectoralis major tendon is identified and released near its insertion with electrocautery. The subscapularis is exposed and isolated from the shoulder capsule near its insertion on the humerus. Release of the subscapularis muscle is performed without violating the glenohumeral joint capsule. The joint capsule should not be opened because instability or intra-articular adhesions may result. The latissimus dorsi and teres major muscles are identified through the interval between the short head of the biceps and deltoid musculature. Release of these deforming muscles can then be performed in a non-functional extremity. A drain is placed deep into the wound prior to closure. Post-operatively, an aggressive mobilization program is instituted following skin healing. Gentle range of motion exercises are employed to correct any remaining contracture. Careful positioning of the limb in abduction and external rotation is necessary for several months to prevent recurrence.

*Selective Shoulder Lengthenings* Muscle overactivity in shoulder extensors and adductors commonly restricts shoulder movement important for reaching. Selective lengthenings to improve reaching are based on clinical examination and dynamic EMG studies. When pectoralis major is involved, an incision is made on the anterior shoulder beginning at the coracoid process and extending distally. The tendinous insertion of pectoralis major

is identified. The pectoralis is lengthened by transecting the tendon where it overlaps with the muscle belly. This junction can be found on the undersurface of the muscle. The tendon must be transected proximally to avoid complete rupture of the muscle tendon unit. The degree of muscle overactivity in the muscle ultimately determines the amount that the muscle tendon unit will lengthen. A new tendon forms within 3 weeks of surgery. When latissimus dorsi and teres major are known to be involved, they are identified through the interval between the short head of the biceps and deltoid musculature and lengthened at the musculotendinous junction. When the long head of the triceps is overactive, it is also lengthened. The long head of the triceps can be exposed and lengthened through the same incision.

After surgery the patient does not need immobilization. Therapy is started on the first post-operative day and consists of active and active assisted movement of the shoulder. No passive stretching or resistive exercises are permitted until 3 weeks after surgery to avoid over lengthening or rupture of the lengthened muscles.

**Supraspinatus Slide** Overactivity of the supraspinatus muscle can cause abduction posturing, making balance while ambulating difficult. The supraspinatus may be effectively lengthened by means of a slide procedure. The patient is placed in the lateral decubitus position with the affected extremity uppermost. An incision is made parallel to the scapular spine. The trapezius insertion is detached from the spine of the scapula, leaving a cuff of fascia for later reattachment. The deltoid is retracted laterally. Using a small periosteal elevator, the origin of the supraspinatus is elevated subperiosteally from the medial border of the scapula. The dissection is continued laterally, with care being taken to avoid injury to the neurovascular pedicle at the suprascapular notch. The muscle is then allowed to slide laterally. The trapezius is reattached to the scapular spine. The patient is allowed full, unrestricted postoperative motion.

### Technique and Post-Operative Rehabilitation of the Elbow

**Selective Flexor Lengthening for Active Function** Elbow extension is an important component of reaching and patients with a flexed elbow pattern have difficulty with reaching and placing the hand in space. When the biceps is involved, a longitudinal incision is made over the proximal anterior arm starting at the lower edge of the pectoralis major tendon. The muscle tendon junctions of both the long and short heads of the biceps are exposed. Tendon tissue that directly overlies muscle belly is then sharply transected, allowing the muscle tendon unit to lengthen (Figure 35-27). When brachialis is involved, an incision is made on the lateral aspect of the elbow. The

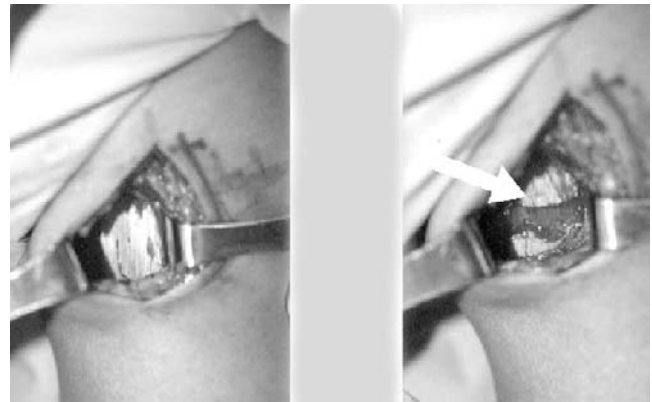


FIGURE 35-27

Lengthening of biceps at myotendonous junction. Photo on left reveals shiny biceps tendon with unseen muscle on its undersurface. Photo on right reveals dissection and separation of tendon, exposing the muscle belly underneath (which is not transected)

brachialis muscle is exposed and lengthened over its' broad muscle tendon junction. Through a separate incision on the radial aspect of the forearm, the myotendinous junction of the involved brachioradialis is identified and lengthened using similar technique.

When the muscles have been lengthened with this method, no immobilization is needed. Active range of motion exercises are started on the first day after surgery. No resistive exercises are allowed for 3 weeks to prevent over-lengthening of the muscles with resulting weakness. Functional elbow flexor lengthening has significantly enhanced the fluid control of elbow motion and improved hand placement in properly selected patients.

**Elbow Flexor Release for Passive Function** Persistent muscle overactivity of the elbow flexors causes myostatic contracture and flexion deformity of the elbow. This results in skin maceration and breakdown of the antecubital space. The position of severe elbow flexion also predisposes the ulnar nerve to an acquired compression neuropathy by increasing the vulnerability to direct pressure and decreasing the cross sectional area of the cubital tunnel. Surgical release of the biceps tendon and brachioradialis muscles and lengthening or release of brachialis is performed depending on the severity of the contracture. The joint capsule is not released. Gradual extension of the elbow with serial casting or physical therapy corrects the pre-operative deformity and decreases the ulnar nerve compression.

Approximately 50% correction of the deformity can be expected at surgery without causing excessive tension on neurovascular structures that are also contracted. Serial casting or drop out casts with electrical stimulation of triceps can be used to obtain further correction over the ensuing weeks.

*Surgical Treatment of Ulnar Nerve Compression* Prolonged elbow flexion with traction on the nerve can lead to decreased volume of the cubital tunnel resulting in nerve compression. Support of the torso by leaning on a chronically flexed elbow may result in direct compression of the nerve. The patients are often limited in their ability to complain about ulnar nerve symptoms because of limited cognitive and communicative abilities. The diagnosis is usually suspected because of intrinsic atrophy, and confirmed using nerve conduction studies. A 2.5% incidence has been shown in patients with traumatic brain injury. Treatment is ulnar nerve transposition, often at the same time as elbow flexor lengthening, or flexor releases. Subcutaneous transposition in the forearm is preferred.

### **Technique and Post-Operative Rehabilitation of the Forearm**

*Fractional Lengthening of Forearm Pronators* Muscle overactivity or contracture of one or both pronators impairs the ability of the forearm to orient objects in the hand toward the body by means of supination. The use of feeding and grooming utensils and clothes fasteners becomes problematic when supination is restricted. Dynamic EMG of pronator quadratus, pronator teres and biceps (to rule out weak supination) is informative. When pronator teres is involved, it is approached in the interval between the mobile wad and the flexor carpi radialis in the mid forearm. Myotendinous lengthening is then performed by cutting the tendinous fibers of the musculotendinous junction and allowing the tendon fibers to slide on the muscle belly, thereby lengthening the muscle tendon unit.

When pronator quadratus is involved, it is approached via an incision over the volar aspect of the forearm just proximal to the wrist crease. The finger flexor tendons are retracted radially to expose the broad myotendinous junction of the pronator quadratus. The tendon fibers are transected, leaving the underlying muscle fibers intact. The forearm is then supinated, separating the ends of the tendon fibers and lengthening the pronator quadratus. No immobilization is used and active exercises are begun immediately after surgery. No passive stretching of the wrist by a therapist is allowed for 3 weeks. Resistive exercises can be started 6 weeks after surgery.

### **Technique and Post-Operative Rehabilitation of the Wrist**

*General Comments* A flexed wrist is common after TBI but hyperextension deformity may also be seen. Patients complain of difficulty inserting their hand into shirts, jackets and other narrow openings and they frequently have pain on passive motion. They may also have symptoms

of carpal tunnel syndrome secondary to compression of the median nerve against the transverse carpal ligament by taut flexor tendons. In severe cases, wrist subluxation may be present. Ulnar (sometimes radial) deviation and a clenched fist are often present as well. When a patient has underlying voluntary control, the surgical treatment for wrist flexion is usually myotendinous lengthening of the wrist flexors. Finger flexors may also be lengthened if they are strongly overactive and contribute to wrist flexion deformity. When the goal is to improve passive function only, selective muscle releases, wrist fusion, proximal row carpectomy and superficialis to profundus tendon transfer may be considered

*Technique of Fractional Wrist Flexor Lengthening* In a limb with volitional control, fractional lengthening of the appropriate wrist flexors is performed. This is done in conjunction with lengthening of the extrinsic finger flexors when indicated. A longitudinal incision is made on the volar surface of the forearm. This incision is extended distally if a carpal tunnel release is necessary. The palmaris longus tendon is divided if tight. A myotendinous lengthening is performed by transecting the tendinous portion overlying the myotendinous junction. No immobilization is used after surgery. The patient is begun on a program of active exercise immediately after surgery. No passive stretching of the wrist by a therapist is allowed for 3 weeks. Resistive exercises can be started 6 weeks after surgery.

*Wrist Flexor Release and Wrist Fusion* When wrist flexion deformities are severe and there is little or no active function seen in the hand, release of the wrist flexors is performed. A proximal row carpectomy may be needed in some patients to correct a severe deformity. Because the median nerve is compressed against the proximal transverse carpal ligament causing painful neuropathy, a carpal tunnel release is performed as well. The wrist is then stabilized with a wrist fusion and is placed in a well-padded splint or cast for six weeks until the fusion has healed. Wrist fusion is done to eliminate the need for a wrist orthosis after surgery. Splints tend to be lost by these patients and their caregivers and, without wrist fusion, gravity alone can cause a recurrence of the flexion deformity.

### **Technique and Post-Operative Rehabilitation of the Hand**

*Fractional Lengthening of Extrinsic Finger Flexors* The clenched fist pattern may have early origins in an unmasking of the primitive grasp reflex. Muscles that contribute to the clenched fist deformity include flexor digitorum sublimis (FDS) and flexor digitorum profundus (FDP). If the proximal interphalangeal (PIP) joints flex while the distal interphalangeal (DIP) joints remain extended, the

'fingernails visible' sign, overactivity of FDS rather than FDP is suspected. When fingernails are not visible because the DIP joints are curled into the palm, overactivity of FDP is also suspected. Dynamic EMG studies have shown that FDS exhibits a marked degree of overactivity while FDP can be minimally overactive with better volitional control. Many patients can have voluntary EMG recruitment in finger extensors but extension is masked by overactive finger flexors that are simply stronger.

Surgery is performed through a longitudinal incision on the volar surface of the forearm, commonly at the same sitting with wrist flexor lengthenings. The palmaris longus tendon is divided. Lengthening of the individual tendons of FDS and FDP is performed by sharply incising the tendon fibers as they overly the muscle belly at the musculotendinous junction, allowing the tendon to slide distally (Figure 35-28). When involved in a thumb-in-palm deformity, the flexor pollicis longus tendon is lengthened in an identical manner. This technique allows the tendons to lengthen with minimal scarring. By transecting the tendon over the muscle belly, no sutures are needed. This eliminates scarring from foreign body reaction to suture material. The underlying support and vascularity of the muscle provides an optimal environment for the tendons to heal and reconstitute themselves.

Post-operatively a wrist splint is used for one week to prevent excessive stretch of the finger flexor. The patient begins a program of active and active assisted exercises on the first post-operative day. For patients with

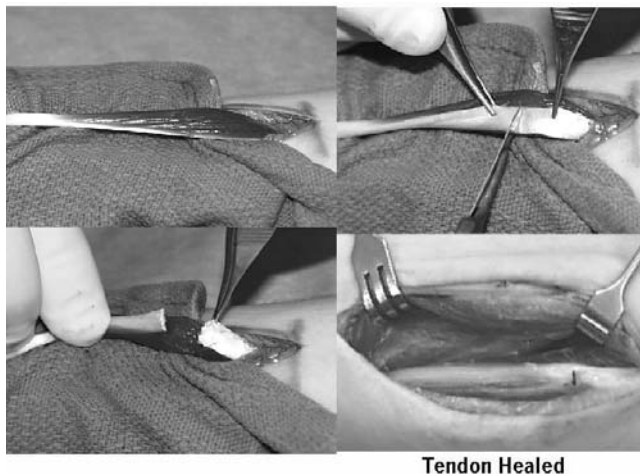


FIGURE 35-28

Technique of fractional lengthening. Muscle and tendon overlap. In the upper right figure, the tendon is exposed and sharply dissected without cutting through muscle tissue. In the lower left figure, the tendon is allowed to slide distally. The underlying support and vascularity of the muscle provides an optimal environment for the tendons to heal at a longer length and reconstitute themselves as seen months later in the lower right figure

limited motor control, it is often useful to use the splint for a longer period to position the wrist while the patient exercises the fingers. The immediate active motion allows the flexor tendons to continue to lengthen in the post-operative period as necessary. Ultimately, the amount of flexor lengthening is determined for each individual muscle by its' underlying tone and control rather than by the surgeon's estimate of tone. Using this technique we have had marked improvement in functional results when compared to our previous regimen of post-operative immobilization (Figure 35-29).

*Superficialis to Profundus Tendon Transfer* In a hand with skin maceration, malodor and pain on passive motion and in the absence of volitional control, more significant lengthening of flexor tendons is obtained with a superficialis to profundus (STP) tendon transfer. This provides a more cosmetically pleasing hand position, aids in hygiene by getting the fingers out of the palm and provides some passive restraint to otherwise unchecked extension.

The superficialis to profundus tendon transfer is performed through a longitudinal volar incision that may be extended distally to allow release of the carpal tunnel and access to Guyon's Canal. The palmaris longus tendon is identified and transected. The four superficialis tendons are sutured together distally and then transected for the en masse transfer. The profundus tendons are sutured together proximally and then cut. The fingers are

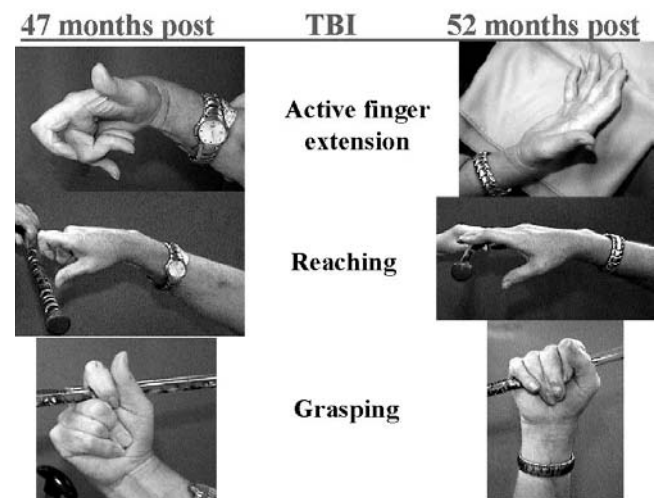


FIGURE 35-29

This patient was seen 47 months after TBI. He had UMN and had developed contracture of the superficial finger flexors. He was able to flex and extend his fingers but the arc of motion was extremely limited. Maximum finger extension is seen in the top left photo. Fractional lengthening of superficial finger flexors and joint capsuloplasties were performed in order to open up the hands. The patient did well postoperatively as seen in the upper, middle and lower right photos

extended and the distal end of the superficialis tendons is then sutured en masse to the proximal end of the profundus tendons.

Several other surgical procedures are routinely done in combination with the superficialis to profundus tendon transfer to treat the concurrent deformities. A neurectomy of the motor branch of the ulnar nerve is needed to prevent an intrinsic plus deformity from developing. If an intrinsic contracture is seen at the time of surgery following the STP lengthening, then release of the intrinsic is also performed. A carpal tunnel release is done to decompress the median nerve. To prevent a recurrent wrist flexion deformity from occurring secondary to passive wrist flexion, the wrist must be stabilized. Wrist extensor tenodesis has been attempted but often will stretch out with time. A cock-up wrist splint can be worn but patient compliance is poor. A fusion of the wrist in 15 degrees of extension provides the most reliable means of maintaining hand position and is now routinely performed. A proximal release of the thenar muscles is often needed to correct a thumb-in-palm deformity but, when needed, it is performed at a later time because STP transfer and wrist fusion are extensive procedures.

Post operatively, the wrist is immobilized for three weeks in a short arm splint which includes the fingers and thumb. The wrist is held in 15 degrees of extension and the fingers are immobilized with the metacarpophalangeal (MCP) joints in 60 degrees of flexion and the interphalangeal joints extended. Gentle range of motion of the MCP joints is started after cast removal. A volar wrist splint is used until the wrist fusion is healed.

### Technique and Post-Operative Rehabilitation of the Thumb

*Thumb-in-Palm Deformity* The thumb-in-palm deformity may result from overactivity in flexor pollicis longus, adductor pollicis (AP), and/or the thenar muscles (particularly flexor pollicis brevis (FPB)). The thumb is held within the palm, the IP joint of the thumb is commonly flexed and the thumb is unable to be positioned for key pinch or three-jaw chuck grasp (i.e. in opposition to the pads of the index and third fingers). Clinically, overactivity of flexor pollicis longus is indicated by flexion of the interphalangeal joint. Adductor pollicis and, sometimes, first dorsal interosseous can narrow the web space. Flexor pollicis brevis contributes to flexion of the metacarpophalangeal joint of the thumb.

*Thenar Muscle Slide* FPL is lengthened as previously described. Under tourniquet control, an incision is made along the thenar crease on the palm. The origins of FPB, opponens pollicis and abductor pollicis are detached from their origins while protecting the recurrent branch of the median nerve. The thumb is extended allowing the

released muscles to slide radially and reattach in an improved position, preserving function and preventing a hyperextension deformity.

The origin of the AP is released from the third metacarpal. Careful dissection to retract the digital neurovascular bundles and flexor tendons to the index and long digits is necessary. The deep palmar vascular arch and deep branch of the ulnar nerve are identified as they penetrate the AP between its oblique and transverse heads prior to adductor muscle release. The neurovascular supply of the AP is preserved. If the first dorsal interosseous muscle is contracted, a release is performed through a dorsal incision along the ulnar margin of the thumb metacarpal while protecting the radial sensory nerve. The origin of the first dorsal interosseous is released from its origin on the base of the first metacarpal. In persistent web space contractures despite appropriate muscle releases, a Z-plasty of the thumb web space is indicated. Post-operatively, the patient is immobilized in a thumb spica cast for 3 weeks. Active therapy is initiated after cast removal to optimize functional results.

### Technique and Post-Operative Rehabilitation of the Pelvis and Hip

*Heterotopic Ossification (HO) of Anterior Hip (Flexor)* After traumatic brain injury, HO typically occurs along lines of tension caused by muscle overactivity. Anterior HO is seen to follow the iliopsoas muscle. Anterior HO usually extends from the anterior superior iliac spine (ASIS) and inner aspect of the pelvis to the proximal femur in the region of the lesser trochanter. Preoperative computed tomography (CT) scans with 3 dimensional reconstruction can be extremely helpful in preparing for the morphology. When resecting anterior hip HO, a standard anterior approach to the hip is performed but the femoral triangle and its contents are also dissected. Care is taken to identify all major divisions of the femoral artery, nerve, and vein. It is prudent to place vascular loops around all major vessels proximally in order to assure easier control of bleeding should a major vessel be damaged during the procedure. A wide exposure and meticulous hemostasis are needed. Although all the neurovascular structures may be encased in HO, it is more common for the nerve to be entrapped. The femoral nerve is already dividing into its many branches within the femoral triangle. The motor branches are small in diameter and must be carefully identified. Because it is difficult to mobilize the neurovascular structures, the heterotopic bone must be removed in small segments. It is difficult to distinguish normal from abnormal bone. The morphology of the normal bone and the HO must be closely observed. A 3 dimensional reconstruction of the hip based on CT scans and intraoperative radiographs are used to guide the resection.

*HO of Medial Hip (Adductor)* Heterotopic bone seen inferomedial to the hip joint follows the adductor muscles from the pubis and extends towards the medial aspect of the femur. A medial approach to the hip is used for resection. If there is a significant hip adduction contracture, release of the hip adductors may also be needed. Often HO is seen both anterior and medial to the hip. In these cases it is necessary to make two separate incisions and work between both.

*HO of Posterior Hip (Extensor)* Posterior HO lies immediately posterior to the femoral head and neck. Although posterior bone forms in conjunction with hip extensor overactivity, it is usually associated with a flexion contracture of the hip. A posterior approach to the hip is used for resection. The sciatic nerve is identified distally and dissected proximally. It is common for the sciatic nerve to be encased within the mass of heterotopic bone. Significant scarring is also seen around the sciatic nerve secondary to the intense inflammatory reaction that occurs during the intermediate stages of bone formation. Neurolysis of the sciatic nerve may be needed. Once the sciatic nerve is identified, a more aggressive resection of the bone is begun. If a significant hip flexion contracture persists after excision of the posterior HO, an anterior soft tissue release may then be necessary.

*HO of Lateral Hip (Abductor)* When HO is seen in the abductor region, it is usually a result of trauma or surgical stimulation. A straight lateral or posterior incision can be used. It is important to separate the heterotopic bone from the abductor muscles and preserve as much muscle function as possible. The abductor muscles are usually very atrophic.

*Obturator Neurectomy for Scissoring Thighs (Hip Adduction Deformity)* Scissoring of the legs in an ambulatory patient gives the patient a narrow base of support while standing and results in poor balance. A preoperative obturator nerve block will eliminate adductor overactivity and allow assessment of adduction contracture. Alternatively, the patient can be examined at the time of surgery while under anesthesia to determine if a fixed myostatic contracture is present. If no adduction contracture is present, transection of the anterior branches of the obturator nerve will denervate the adductors and allow the patient have a broader base of support. A longitudinal incision is made directly over the adductor longus muscle. Commonly, a small contracture is present and the adductor longus muscle is released and retracted. The anterior branch of the obturator nerve is then transected over the muscle belly of the adductor brevis. Early gait training with weight bearing as tolerated is instituted in the postoperative period.

*Hip Adductor Tenotomy for Severe Contracture* Indications for surgical release of hip adduction contracture

include interference with perineal care and hygiene in a non-ambulatory patient and excessive limb scissoring during attempted transfers and ambulation in a patient with active function. Hip flexion contracture is a frequent accompaniment (see next section). With the patient in the supine position, a longitudinal incision is made over the adductor longus muscle. The incision is made distal to the groin crease in a more hygienic location. The adductor longus muscle is dissected free and transected using electrocautery. The anterior branches of the obturator nerve are identified and transected. The adductor brevis and gracilis are released close to their origin on the pubis. The wound is closed over a drain. Daily wound care is essential to prevent infection in this potentially contaminated area. The hips should be kept in abduction for 4 weeks using casts or an abduction pillow splint to prevent recurrence of the deformity during wound healing.

*Functional Hip Flexor Release* Muscle overactivity in the hip flexors can result in a crouch gait with compensatory knee flexion to maintain balance. This is a very costly deformity since it requires constant use of the quadriceps, hip extensor, and calf muscles to maintain upright posture. The energy requirement for continuous firing of these muscles is extremely high. Few patients are able to remain ambulatory with this deformity. The hip flexor muscles are needed to advance the limb during gait. Therefore, complete release of the hip flexors should be avoided in any patient with potential to ambulate. Since the iliopsoas has capsular insertions, release of the iliopsoas tendon from the lesser trochanter of the femur does not provide a complete release. Release of the tendon from the lesser trochanter permits the iliopsoas to recess proximally, diminishing its pull but retaining its function.

A medial approach to the hip is used. A longitudinal incision is made overlying the adductor longus tendon. The adductor longus is released since it contributes to hip flexion. The pectineus muscle is identified where it lies deep to the femoral vessels and medial to the adductor longus. The pectineus muscle is divided using electrocautery. The lesser trochanter of the femur can be palpated in the depth of the wound. The tendon of the iliopsoas is visualized by placing narrow reverse retractors above and below the lesser trochanter. The iliopsoas tendon is divided from the trochanter and allowed to retract proximally. The wound is closed over a drain. Postoperatively, the patient begins range of motion exercises and full weight bearing gait training as tolerated. Prone lying and electrical stimulation of the gluteus maximus muscle are helpful to correct any residual hip flexion deformity.

*Non-Functional Hip Flexor Release* In a non-ambulatory patient, indications for surgical release include hip flexion contracture or severe muscle overactivity causing poor hygiene or pressure sores that cannot be healed

because of limited positioning of the patient. When a severe adduction contracture of the hip is present, it may be necessary to perform a percutaneous release of the adductor longus tendon in the groin in order to position the patient adequately and prep for further surgery. Any flexion contracture of the knee should be corrected simultaneously to prevent the leg from positioning in flexion and causing a recurrent and more resistant contracture.

With the patient in the supine position an anterior incision is made beginning just below the anterior superior iliac spine and is carried distally following the sartorius muscle for a short distance. The lateral femoral cutaneous nerve is identified as it passes distal to the anterior superior iliac spine and protected. The sartorius muscle is detached from its origin on the anterior superior iliac spine. The rectus femoris muscle is released from its origin on the anterior inferior spine of the pelvis. The femoral nerve and vessels are gently retracted medially to expose the iliopsoas muscle on the anterior aspect of the hip. The iliopsoas and pectineus muscles are carefully divided over the pelvic brim using the electrocautery to diminish post-operative bleeding. Since the iliopsoas has capsular insertions, release of the iliopsoas tendon from the lesser trochanter of the femur does not provide a complete release. The tensor fascia lata and the anterior portion of the gluteus medius and gluteal aponeurosis may be released from the iliac crest, if necessary. The hip joint capsule is not released.

In a severely contractured patient, care must be taken to identify all structures prior to release since the anatomy is frequently distorted by the long-standing deformity. A large dead space is left after releasing the hip flexor muscles and a drain should be used. Careful wound closure and a compressive dressing are helpful in preventing post-operative infection. As with release of other contractured joints, approximately 50% of the deformity will be corrected at the time of surgery. Daily wound care will help prevent infection in this area where bacterial contamination is likely and a large dead space remains following surgery. Placing the patient in a prone position three times a day for increasing periods and gentle stretching exercises will assist in correcting any residual hip flexion deformity. When release of a knee flexion contracture has been performed simultaneously, the weight of the long leg cast will also provide a correcting force. Sitting in a wheelchair is allowed for short periods.

### **Technique and Post-Operative Rehabilitation of the Knee**

*Distal Hamstring Lengthening* A knee flexion deformity is caused by overactivity of the hamstring muscles. A lengthening procedure is done when the knee flexion deformity is less than 60 degrees and the patient has documented volitional activity in the hamstrings. This will

correct the flexion deformity while preserving function of the hamstrings. With the patient in the supine position, a longitudinal incision of approximately 8 cm. is made on the lateral aspect of the distal thigh just proximal to the knee joint. The peroneal nerve is isolated and protected and the biceps femoris tendon is divided obliquely as it overlies the muscle belly. This allows the tendon to slide distally while still maintaining continuity of the muscle. The portion of the iliotibial band that is posterior to the axis of knee flexion is also divided transversely.

A longitudinal incision is then made on the medial aspect of the distal thigh. The tendons of the gracilis and semimembranosus are isolated and fractionally lengthened at the myotendinous junction by making an oblique cut in the tendon as it overlies the muscle belly. The semitendinosus tendon has a very short myotendinous junction that does not permit fractional lengthening. This tendon is simply transected.

After surgery, the extremity is immobilized in a long leg cast. Approximately 50 percent correction of the knee flexion deformity can be expected at the time of surgery. Further correction is limited due to tethering of the neurovascular structures. The extremity is casted in the position of knee extension it assumes while being supported under the heel, without attempting forced extension. Forced knee extension can result in limb ischemia. The long leg cast is changed weekly until full knee extension has been obtained. Splints are used at night for an additional 4 weeks to maintain correction.

*Distal Hamstring Release* In a non-ambulatory patient with a marked increase in hamstring muscle tone, knee flexion contractures result. When severe hamstrings overactivity and/or a knee flexion contracture greater than 60 degrees is (are) present, attempts to correct knee position with casting or bracing may result in posterior subluxation of the tibia. With the patient supine, distal hamstring release begins with a longitudinal incision made on the lateral aspect of the distal thigh just proximal to the knee joint. The peroneal nerve is isolated and protected and the biceps femoris muscle and tendon are divided just proximal to its insertion using electrocautery. The portion of the iliotibial band that is posterior to the axis of knee flexion is also divided transversely.

A longitudinal incision is then made on the medial aspect of the knee and the tendons of the gracilis, semimembranosus and semitendinosus are isolated and divided. In severe contractures, release of the sartorius muscle is also performed. By using electrocautery the procedure is easily performed without a tourniquet, which facilitates localization and protection of the posterior tibial artery, vein and nerve. Following localization of the neurovascular bundle, any remaining restricting bands are divided as required. The posterior fascia at the knee is often thickened limiting extension and may require



release. The posterior joint capsule may need to be released in long standing contractures. The joint capsule is stripped from the distal posterior femur using a periosteal elevator. The cruciate ligaments are not divided. If more correction is required, a closing wedge osteotomy can be performed. A closing wedge will allow for some shortening of the femur and some release of tension from the neurovascular structures and posterior skin.

After surgery the extremity is immobilized in a long leg cast. Approximately 50 percent correction of the knee flexion deformity can be expected at the time of surgery. Further correction is limited due to tethering of the neurovascular structures. The extremity is casted in the position of knee extension it assumes while being supported under the heel, without attempting forced extension. (Forced knee extension can result in limb ischemia.) If a severe hip flexion deformity is not corrected at the same time as the hamstring release, recurrent knee flexion contracture, resistant to surgical correction, is likely to develop.

Postoperatively, the long leg cast is changed weekly until full knee extension has been obtained. Splints or a knee immobilizer are used at night for an additional 4 weeks to maintain correction. Distal release of the hamstring tendons does not prevent ambulation.

### KNEE EXTENSION DEFORMITY

*Rectus Femoris to Gracilis Transfer for Dynamic Stiff Knee Gait* Patients with a stiff knee gait are unable to flex their knee during swing phase. The impairment is dynamic meaning that it only occurs during walking. There is no restriction of passive knee motion and the patient does not have difficulty sitting. Toe drag, which is likely in the early swing phase, may cause the patient to trip: thus balance and stability are also affected. A gait study with dynamic EMG commonly reveals dyssynergic activity in rectus femoris and vastus intermedius. If knee flexion is improved with a block of the rectus femoris or vastus intermedius, the rationale for surgical intervention is strengthened. Any equinus deformity of the foot should be corrected prior to evaluation of a stiff knee gait since equinus causes a knee extension during stance that may carry over to swing. Since the degree of knee flexion during swing is directly related to the speed of walking, the patient should be able to ambulate with a reasonable velocity in order to benefit from surgery. Good hip flexion strength is also needed for improved knee flexion since it is the forward momentum of the leg that normally provides the inertial force to flex the knee.

The rectus to gracilis transfer begins with a longitudinal incision that is made on the anterior thigh from mid-thigh to the middle of the patella. The rectus femoris muscle is dissected free from the other vasti muscles. Dissection is carried distally to the patella where a strip

of periosteum is also removed from the patella to gain additional length. If significant overactivity was seen in the vasti muscles on the dynamic EMG study, these muscles are fractionally lengthened by transecting their tendons as they overly the muscle belly.

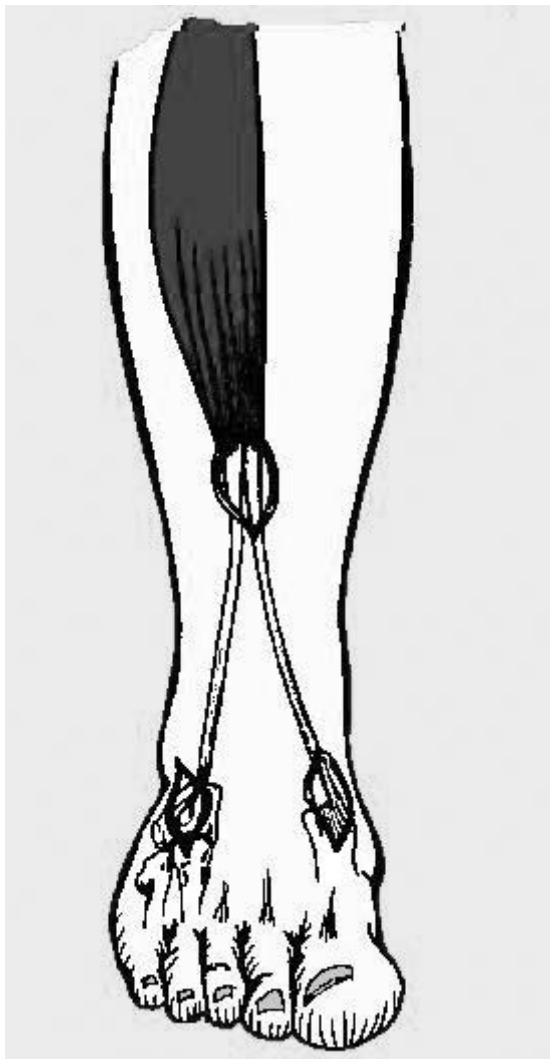
A second incision is made over the medial hamstrings just proximal to the knee. The gracilis tendon is identified and released proximally. This provides a distal length of tendon to attach to the transferred rectus femoris. A subcutaneous tunnel is then made between the two incisions and through the intermuscular septum. The distal end of the rectus femoris tendon is passed through the tunnel to the medial wound with the knee flexed 90 degrees and the femur externally rotated. The rectus femoris tendon is sewn to the gracilis tendon.

The patient is placed in a knee immobilizer splint for one week after surgery to prevent a knee flexion deformity from occurring secondary to the tension and discomfort of the transfer. The patient can begin gait training in the immobilizer on the first postoperative day. Because of the good fixation into the gracilis tendon, knee range of motion and ambulation without the splint is started one week later. A marching gait pattern is stressed during therapy to facilitate knee flexion during swing.

### Technique and Post-Operative Rehabilitation of the Foot and Ankle

*Achilles Tendon Lengthening for Equinus* The commonest upper motoneuron deformity causing gait difficulty is equinus. An equinus deformity may be static secondary to contracture or dynamic secondary to muscle overactivity of the gastrocnemius and soleus muscles. This deformity prevents initial heel contact, promotes knee hyperextension, hyperextension thrust and knee pain in early stance and impedes rollover and push-off in late stance. Surgical lengthening of the Achilles tendon is indicated when the patient's foot and ankle position is not adequately controlled by an orthosis or when attempting to make the patient brace free. Adequate lengthening of the Achilles tendon can be performed using the Hoke triple hemisection technique percutaneously. With the foot held in maximum dorsiflexion, three percutaneous hemi-transections of the Achilles tendon are made. If a varus deformity of the foot is present, the proximal and distal cuts are made in the medial half of the tendon and the center cut is placed laterally. The foot is then pushed into dorsiflexion allowing the tendon to lengthen. Postoperatively, the patient is placed in a short leg walking cast at surgery, holding the foot in a neutral position. Gait training can be started on the first postoperative day allowing the patient to bear full weight on the foot as tolerated. Postoperative management requires 6 weeks of rigid immobilization. After this the patient uses a molded, high resistance, ankle-foot orthosis for an additional 6 weeks.

*Split Anterior Tibialis Tendon Transfer (SPLATT) for Varus* Varus deformity of the foot promotes unstable weightbearing on the lateral border of the foot during the loading response subphase of gait. It also renders brace wear difficult or impossible. Varus deformities most commonly occur as a result of increased and inappropriate activity of the tibialis anterior (TA) muscle. When dynamic EMG has documented tibialis anterior as a source of varus, the deformity is corrected by a SPLATT. The SPLATT maintains half of the TA tendon on the medial aspect of the foot and transfers the other half of the TA tendon to the lateral side of the foot (Figure 35-30). Varus deformity is usually accompanied by equinus as



**FIGURE 35-30**

When tibialis anterior is a source of varus, the deformity is corrected by a split anterior tibialis tendon transfer (SPLATT). The SPLATT procedure maintains half of the tibialis anterior (TA) tendon on the medial aspect of the foot and transfers the other half of the TA tendon laterally into the cuboid bone

well as toe curling due to overactivity of extrinsic and intrinsic toe flexor muscles. Lengthening of the Achilles tendon should be performed first, followed by division of toe flexor tendons.

The SPLATT begins with an incision made over the distal insertion of the TA on the medial aspect of the foot. The lateral half of the tendon is sharply divided from its insertion. An absorbable suture is placed at the end of the tendon for ease of handling. A second incision is made on the anterior distal third of the leg just lateral to the crest of the tibia over the TA muscle. An opening is made in the fascia overlying the TA. We use a long twisted wire loop as a tendon passer. The wire loop is passed under the fascia and follows the TA tendon to the incision on the medial foot. The suture in the free end of the tendon is passed through the wire loop and is pulled into the proximal wound. This suture is used to pull the free end of the tendon into the proximal wound thereby splitting the TA tendon and a portion of the muscle belly.

A third incision is then made on the lateral aspect of the foot. The cuboid is exposed. A 5 mm drill is used to make a tunnel through the cuboid. The TA tendon is passed subcutaneously to the lateral foot incision. A straight needle is used to pull the suture and then the TA tendon into the bony tunnel of the cuboid. With the foot held in a corrected position, the tendon is then secured in the cuboid by placing an absorbable 7 mm interference screw in the tunnel adjacent to the tendon. The free end of the suture is trimmed at skin level. To correct curl toes, a longitudinal incision is made on the plantar surface of each toe at the level of the metatarsophalangeal joints. The flexor tendons are identified and released under direct vision. This procedure is commonly done in combination with an Achilles tendon lengthening since bringing the foot into a plantigrade position will worsen toe curling. When an Achilles tendon lengthening has been performed, the foot must be immobilized as described above.

Postoperatively the patient is placed in a short leg walking cast at surgery holding the foot in a neutral position. Gait training can be started on the first postoperative day allowing the patient to bear full weight on the foot as tolerated. The cast is kept on the foot for 2 weeks. Two weeks after surgery the cast and sutures are removed. The patient is then placed in a cam walker boot for the next 4 weeks (Figure 35-31). With reliable patients we allow the cam boot to be removed once daily for washing and skin care. The foot must be maintained in a neutral position while the boot is off and now weight bearing is allowed. Six weeks after surgery the patient begins using a non-articulated, moderately rigid ankle foot orthosis for an additional 6 weeks. The patient must sleep wearing AFO during this time to protect the foot from an inadvertent stretch. At 3 months after surgery the brace can be removed for sleeping and gait training. The

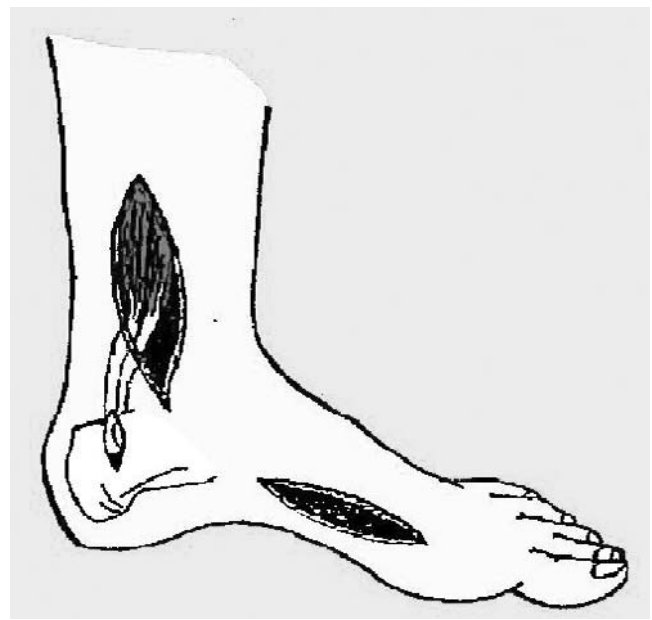


**FIGURE 35-31**

Patient in a cam walker boot. When an Achilles tendon lengthening has been performed, the foot is initially immobilized in a walking cast for 2 weeks. Two weeks after surgery, cast and sutures are removed and the patient is placed in a cam boot for the next 4 weeks. The cam boot can be removed once daily for washing and skin care. Six weeks after surgery the patient begins using a nonarticulated, moderately rigid ankle foot orthosis for an additional 6 weeks

AFO can be discontinued if and when the patient has established sufficient strength in the calf muscles to permit safe walking.

*Tibialis Posterior (TP) Lengthening* In a small percentage of patients, TP is also overactive and can contribute to varus deformity. Clinically, increased heel varus is observed in addition to forefoot varus caused by TA. When overactivity of TP is present, a myotendinous lengthening of the tendon is performed posterior and slightly proximal to the medial malleolus. Complete release of the tibialis posterior tendon is not recommended as a planovalgus deformity may occur secondarily.



**FIGURE 35-32**

Achilles tendon lengthening to correct equinus weakens the gastrocnemius-soleus muscle group. Transfer of FDL into the os calcis can be done to augment calf strength. The figure depicts the transfer beginning with an incision on the medial border of the foot, dorsal and parallel to the abductor hallucis muscle. With this transfer, more patients eventually achieve brace free ambulation (see text)

*Transfer of the Flexor Digitorum Longus (FDL) to Os Calcis* Muscle paresis (weakness) is a classic negative sign of the upper motoneuron syndrome. Lengthening the Achilles tendon to correct an equinus deformity weakens the gastrocnemius-soleus muscle group, which was already weak as a consequence of the underlying upper motor neuron syndrome. Calf weakness generally requires an ankle foot orthosis (AFO) during ambulation but transfer of FDL into the os calcis can be done in order to augment calf strength. With this transfer, more patients eventually achieve brace free ambulation. In prior studies of equinovarus foot deformity, 30 percent of patients were able to walk safely without an AFO. When gastroc-soleus strength is augmented by transfer of FDL into the os calcis, 70 percent of patients achieve brace free ambulation.

The transfer begins with an incision on the medial border of the foot dorsal and parallel to the abductor hallucis muscle (Figure 35-32). The abductor hallucis is reflected plantarward from the base of the first metatarsal and flexor hallucis longus (FHL) and FDL are isolated through the deep fascia at the master knot of Henry. At this level, FDL has not yet split into four tendons and FHL is easily dissected free. If the flexor brevis tendons are to be released simultaneously to correct toe curling, they are released prior to transecting the FDL tendon. FHL and FDL are dissected at the knot of Henry.

A second incision is then made at the medial supra-malleolar region where the muscle belly of the FDL is isolated with its tendon and delivered through the medial supramalleolar incision. A one centimeter incision is made over the medial posterior superior aspect of os calcis. A 5mm drill is used to create a tunnel through the posterior superior calcaneus that exits on the lateral side. A suture ligature is placed in FDL and the tendon is passed subcutaneously to the medial heel wound. Using a straight needle attached to the tendon suture, the tendon is then passed mediolaterally through the tunnel created in the os calcis. With the foot held in maximum dorsiflexion, the tendon is secured in the bony tunnel using an interference screw. Holding the foot in maximum dorsiflexion while tensioning the transferred tendon prevents a recurrent equinus deformity.

Postoperatively, the patient is placed in a short leg walking cast at surgery with the foot held in a neutral position. Gait training can be started on the first post-operative day and the patient is allowed to bear full weight on the foot as tolerated. The cast is kept for 2 weeks after which the cast and sutures are removed. The patient is then placed in a cam walker boot for the next 4 weeks. With reliable patients, we allow the cam boot to be removed once daily for washing and skin care. The foot must be maintained in a neutral position while the boot is off and now weight bearing is allowed. Six weeks after surgery the patient begins using a non-articulated, moderately rigid ankle foot orthosis for an additional 6 weeks. The patient must sleep wearing an AFO during this time to protect the foot from an inadvertent stretch. At 3 months after surgery, the brace can be removed for sleeping and gait training. The AFO can be discontinued if and when the patient has established sufficient strength in the calf muscles to permit safe walking.

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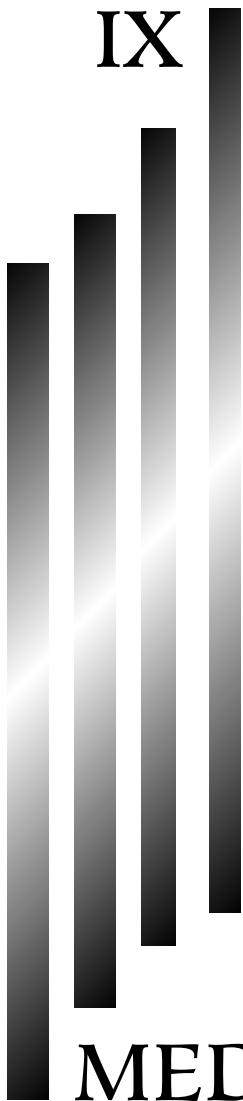
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IX



**MEDICAL MANAGEMENT  
ISSUES**



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# 36

## Gastrointestinal and Nutritional Issues

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**D**epending on the extent of neurological injury, the spectrum of gastrointestinal and nutritional ramifications can be vast. Often the patient who has suffered a traumatic brain injury (TBI) or a spinal cord injury (SCI) is well nourished prior to the injury; however, hypermetabolism resulting from an injury can quickly deplete nutritional stores, especially protein, resulting in a nitrogen death (1).

Many other gastrointestinal (GI) and nutritional problems are common and predictable. Knowledge of their occurrence and protocols for their prevention can help limit their impact on patients. This chapter discusses the GI and nutritional problems that can befall the patient with TBI in the acute and chronic phases of injury. Patients with SCI in addition to TBI may complicate the overall care, and the care of patients with SCI will generally not be discussed in this chapter. However, older references may not have delineated between the two patient populations of TBI with and without SCI. Thus, we will attempt to highlight some of the short comings in our present knowledge of patients with TBI.

### BACKGROUND

The interrelationships of gastrointestinal and nutritional reactions to TBI were not appreciated for many years.

Although Drew et al. reported on the rapid nutritional deterioration after craniotomy in 1947, it was not until 1975 that hypermetabolism was correlated with TBI (2, 3). It was noted that many patients tolerated gastric feeding poorly and widely regarded that hyperosmolar parenteral solutions could worsen cerebral edema (4). Thus, many patients succumbed to their neurological illness or injury, not so much from the initial insult, but from the lack of subsequent feeding during the hospitalization. Furthermore, it was not until 1983 that Rapp and colleagues showed that there was a higher survival rate in patients feed early by total parenteral nutrition (TPN) rather than by attempts at intragastric feeding (5). This was an important conceptual advance since it dispelled the myth that the hyperosmolar TPN solutions would exacerbate cerebral edema, and thereby increase morbidity and mortality.

The actual molecular and cytokine reactions to TBI are beyond the scope of this chapter. However, certain GI or nutritional problems may be associated with changes in hormonal actions that are important to recognize. These will be highlighted with their physiologic consequences.

### GASTROINTESTINAL COMPLICATIONS

Gastrointestinal complications should be separated into conditions that are associated with acute injury and later

events. There will also be some differences when there is also an associated spinal cord injury.

### Gastritis/Erosions/Ulcers

Depending upon the severity of the neurological damage, there appears to be an increased incidence of acute GI erosive lesions in the stomach. A prospective study by Kamada et al. demonstrated a higher rate of gastroduodenal lesions (6). Up to 75% of patients had lesions that were mostly in the stomach (78%). Erosive gastritis was the most common lesion and was often found in the first week after the injury. The use of steroids did not seem to affect the incidence of gastritis. However, it should be noted that this study was performed prior to the commonplace usage of H<sub>2</sub>-receptor antagonist blockers or proton pump inhibitors and the advent of early enteral feeding, all of which may ameliorate this type of injury.

The risk of gastric ulceration from TBI has also been well described and may be the result of another mechanism unrelated to the high incidence of stress gastritis previously mentioned. It has been reported that there is gastric acid hypersecretion which can be the direct result of the elevated serum gastrin levels that have been seen in patients with head injury (7). While gastric ulceration is well known after traumatic injuries, those associated with brain injury have

been noted to be potentially quite severe and may progress to perforation. These have been referred to as Cushing's ulcers (8). Since gastric acid hypersecretion can be controlled with either H<sub>2</sub>-receptor antagonist blockers or proton pump inhibitors, initial care protocols for the patient with TBI should include one of these classes of medications to control intragastric pH. Table 36-1 lists commonly used protocols; note that these may not be specifically approved by the Food and Drug Administration (FDA), but rather what is commonly used in clinical practice (9–14).

### Delayed gastric emptying

Delayed gastric emptying or gastroparesis can occur either with isolated head injury, as previously mentioned, or with cervical spinal cord injuries (15,16). This has ramifications for both nutrition and general care as some patients may experience severe gastric stasis or dilatation that may require nasogastric decompression. Ileus is variably present, but appears more commonly in patients with spinal cord pathology (17). Since the enteric nervous system and smooth muscle layers are still intact, promotility agents should be useful. Unfortunately due to concerns over cardiovascular side effects, cisapride has been removed from the market for common usage. Although it is still available under strict protocol for compassionate usage

**TABLE 36-1**  
*Control of Intragastric pH in Prevention of Stress Gastritis/Erosions/Ulcers\**

ROUTE	MEDICATION	USUAL PROTOCOL
<b>Histamine-2-Receptor Antagonists (H<sub>2</sub>RA)</b>		
IV	Cimetidine** (Tagamet)	300 mg bolus, 50 mg/ hr continuous infusion; Creatinine Clearance (CrCl) < 30ml/min reduce dose by 50%
	Famotidine (Pepcid)	20 mg bolus, 40 mg every 24 hours continuous infusion (or 20 mg every 12 hours) (CrCl) < 50ml/min reduce dose by 50% or increase interval to every 36–48 hours
	Ranitidine (Zantac)	50 mg bolus, 150–200 mg every 24 hours continuous infusion (or 50 mg every 8 hours) (CrCl) < 50ml/min 50mg every 18–24 hours, give more frequently every 12 hours, as necessary
<b>Proton Pump Inhibitors (PPI)</b>		
Enteral	Lansoprazole suspension (Prevacid)	30 mg every 12 hours
Enteral	Omeprazole suspension (Prilosec)	40 mg bolus, repeat 40 mg dose in 6 hours, then 20 mg daily (or 40 mg/ day or 20 mg every 12 hours)
	Pantoprazole IV (Protonix)	40 mg every 12 hours (some centers bolus with 80 mg initially)

\*Table created from references 9–14. Trade name in parentheses.

\*\*Currently the only FDA-approved agent for stress ulcer prophylaxis, often not preferred clinically as the first line H<sub>2</sub>RA due to drug interactions

as an investigational limited access study drug which requires an Institutional Review Board protocol and approval, it is less likely to be used in the initial care of the TBI/SCI patient. With further study it may have been preferred over metoclopramide due to its lack of CNS side effects, but limited data exists in patients with TBI (18). Metoclopramide is presently the only FDA-approved promotility agent. Unfortunately, its use may be limited by its potential for CNS side effects due to its central dopaminergic blocking activity. The drug should not be used in epileptics since the severity and frequency of seizures may be increased. Also, patients that are receiving medications that can increase the risk of extrapyramidal side effects should avoid this medication. Published experience with metoclopramide in TBI is limited and consists mostly of case reports (19).

Erythromycin is a macrolide antibiotic that is structurally similar to the GI hormone motilin. It has been used very effectively as a promotility agent, but as an off-label use and not as a FDA-approved indication. There are currently no known trials of its use for this indication in patients with TBI.

Domperidone is another promotility agent that is available outside the United States. It has not been approved for sale in the U.S., but can often be obtained from pharmacies in Canada or Mexico or even as a compounded, unapproved medication from some pharmacies in America. Thus, inpatient use is unlikely, but it may be useful in carefully selected outpatients.

### Diarrhea and Constipation

Diarrhea is not a common finding in patients with TBI. Thus, patients who have diarrhea should be investigated like any other patient who presents with this symptom. Table 36-2 lists some of the key elements in investigating the cause of diarrhea. If the patient is hospitalized and/or has recently, up to six weeks, received antibiotics, then the standard workup should include stool for white blood cells, investigation for ova and parasites, and stool cultures that include testing for *Clostridia difficile*. Flexible sigmoidoscopy or colonoscopy may be required in some patients.

Other causes of diarrhea must also be considered. The administration of liquid versions of medications may contain sorbitol, which even in modest amounts can cause diarrhea. Antacids may contain magnesium and other medications, like lactulose, are commonly used. Many other drugs may have diarrhea as a side effect, and medication profiles should be reviewed carefully for potential clues.

Diarrhea is the most common complication of enteral tube feeding; however, reports have varied in the incidence from 2.3–68% (20–22). Differences in definitions by various investigators make many studies difficult

**TABLE 36-2**  
**Diarrhea**

#### QUESTIONS TO CONSIDER

How is "diarrhea" being defined?  
Is there a new fever?  
Has the patient received antibiotics in the past 6 weeks?  
Is the patient being tube fed?  
What medications are being given to the patient, especially liquid meds?  
Does the patient have diabetes mellitus?  
Are there any GI complications that could lead to diarrhea?  
Does the patient have a malabsorptive disorder?  
Is the diarrhea "secretory" or "osmotic"?  
Is there visible or occult blood in the stool?  
Is there a history of inflammatory bowel disease, radiation therapy or ischemic bowel?  
Is there a pre-existing motility disorder?

#### STANDARD WORKUP – VARIES WITH THE CLINICAL SITUATION\*

Complete Blood Count (CBC), Erythrocyte Sedimentation Rate (ESR)  
Serum chemistries  
Thyroid studies  
Giardia antigen\*  
Clostridia difficile toxin\*  
Stool cultures, including *Shigella*, *Salmonella*, *Yersinia* and *Clostridia difficile*  
Stool for ova & parasites  
Stool examination for blood

#### MORE INVOLVED WORK-UP

Gastrointestinal Consultation  
Intake & Output measurements  
Endoscopic procedures  
Radiologic investigations  
Stool for osmolality

to compare or interpret. It may be that the actual genesis of diarrhea in these patients is multifactorial. Etiologies can include concurrent use of antibiotics or diarrhea-inducing medications, formula composition, rate of infusion, altered bacterial flora, enteral formula contamination, and hypoalbuminemia (23, 24). Additionally, it appears that the more critically ill patients seem to experience a higher incidence of tube feeding-related diarrhea (22). Initiation of feedings at slower rates until tolerance is seen can help limit this problem.

Blood in the stool must also concern the clinician to look for inflammatory causes or ischemic bowel. Occult blood in the stool is a nonspecific finding, but may

require a more throughout investigation and gastrointestinal consultation. Etiologies are numerous and are beyond the scope of this review.

Constipation can be a much more serious problem in the TBI/SCI patients. Patients who have spinal cord lesions above the fifth thoracic root can experience autonomic dysreflexia which can be a life threatening event. Either bladder distention or fecal impaction can precipitate this abnormal autonomic reflex that can lead to tachycardia and severe hypertension (25). Treatment must be prompt since subarachnoid hemorrhage, stroke or seizures can occur. These patients should be managed with prevention of constipation and routine bladder catheterization to avoid this complication.

### Gallbladder Disease

Acute acalculous cholecystitis is an often unrecognized and a potentially fatal complication that may develop among patients hospitalized for trauma. The cause, although not yet clearly defined, is believed to be multifactorial, resulting from bile stasis, ischemia, bacterial infection, sepsis, narcotics (opiates) that induce sphincter of Oddi spasticity and the activation of factor XII (26). Mortality rates of 10–75% have been reported. That high mortality is attributed to the fact that the gallbladder disease (i.e., necrosis, gangrene, or perforation) is frequently advanced by time of diagnosis. The symptoms and signs are not much different from those of cholecystitis with stones, the most common being right upper quadrant pain, fever, and leukocytosis. However, in the post-traumatic neurosurgical patient, obtundation or neurological deficits can make these valuable physical findings hard to detect (26, 27). Most reports showed that symptoms usually begin between 1–4 weeks after the trauma. The most important factor in early diagnosis of this condition is the clinician's awareness of abnormal laboratory findings and any unexplained deterioration of a previously improving posttraumatic course. Suggestive laboratory findings include elevated serum bilirubin, alkaline phosphatase, liver enzymes and leukocytosis; suggestive physical findings consist of fever, vomiting, abdominal distention, ileus, and in some cases palpable right upper quadrant mass (28, 29).

Ultrasonography is the investigation of first choice and strongly recommended whenever acalculous cholecystitis is suspected. Additional radiologic studies should include plain abdominal X-ray, which is useful predominantly to exclude a perforated viscus, bowel ischemia, or renal stones. Another advantage of ultrasonography includes its ability to examine the liver, pancreas, kidneys, and bile ducts in addition to the gallbladder (30, 31). Ultrasonographic features suggestive of acalculous cholecystitis may include the following: 1) absence of gallstones or sludge; 2) thickening of the gallbladder wall (>5 mm)

with pericholecystic fluid; 3) a positive Murphy's sign induced by the ultrasound probe; 4) failure to visualize the gallbladder; 5) emphysematous cholecystitis with gas bubbles arising in the fundus of the gallbladder (champagne sign); and, 6) frank perforation of the gallbladder with associated abscess formation.

On the other hand, in a retrospective study Puc and coworkers questioned the utility of ultrasonography and found that abdominal ultrasound was sensitive only in 30% and specific in 93% of 62 trauma patients who underwent cholecystectomy for suspected acute acalculous cholecystitis (32). In stable patients in whom the diagnosis is unclear after ultrasonography, radioisotope HIDA scan may be useful. HIDA is an iminodiacetic acid derivative, which is given by intravenous injection, taken up by hepatocytes, and excreted into bile with concentration in the gallbladder. Failure to opacify the gallbladder is indicative of cystic duct obstruction or necrosis with very high sensitivity up to 100% and 90% specificity. Leakage into the pericholecystic space suggests perforation. HIDA should not be recommended in critically ill patients in whom a delay in therapy can be potentially fatal (30, 33). Treatment should be instituted promptly, intravenous broad spectrum antibiotics should be started, and emergent cholecystectomy is now believed to be the treatment of choice. Although cholecystostomy has been advocated, it should be only reserved for the sickest patients not tolerating surgery (26, 27, 34). In a series reported by DuPriest et al, a gangrenous gallbladder was found in 52% of cases (35).

### Pancreatitis

Elevations of serum amylase and lipase have been described in patients in the neurointensive care setting. Hyperamylasemia has been observed in 19–41% of patients with severe head injury and in 45–60% of patients with intracranial bleeding from head trauma with no clinical signs or symptoms of pancreatitis (36, 37). However, making the diagnosis of acute pancreatitis can be difficult in this patient population. These patients often suffer from altered mental status or require therapeutic sedation +/-or paralysis to reduce intracranial pressure, so the clinical information obtained from the physical examination may not always be accurate. In addition, it is not clear whether this enzyme elevation is due to head trauma itself, intracranial bleeding, or some nonspecific intracranial event. Proposed causes include vagal stimulation, altered modulation of the central control of pancreatic enzyme release, and release of cholecystokinin from the brain (36, 37). To investigate the role of intracranial events in patients with TBI, Justice et al. prospectively studied 38 patients admitted to their neurointensive care unit with traumatic intracranial bleeding for elevations of pancreatic enzymes (38). Twenty-five patients (66%) had

elevated lipase enzyme activity, and 17 of the 25 also had elevated amylase without any evidence of clinical pancreatitis. Most lipase elevations occurred earlier than those of amylase, and there was significant interaction between lipase elevation and decreasing Glasgow Coma Score (GCS), indicative of increasing severity of intracranial bleeding (38). Similar findings were seen in a retrospective study by Liu and coworkers of 75 patients with TBI from Cook County Hospital where none of the patients with elevated serum lipase and amylase had any clinical or radiographic evidence of pancreatitis (37). In summary, because of the lack of their diagnostic value, routine pancreatic enzyme monitoring should not be performed in this patient population unless it is clinically indicated, and physician awareness of the association between intracranial bleeding with elevation of pancreatic enzyme of no significance can save the patient needless cost and manipulation.

### Other Less Frequent GI Problems

There are several other GI problems that occur in the patients with TBI and/or SCI, but they are less common than the other problems already discussed. The first two of these can be considered extensions of the altered bowel function that can occur with constipation and less commonly with TBI unless the patient is at a low level of function. Over time, diverticulosis can occur in these patients and lead to the usual complications of this disease; diverticulitis and/or diverticular hemorrhage (17). In the chronic SCI patient, this may be particularly problematic as the abdominal presentation may be altered and even delayed, leading to an acute abdomen in cases of diverticulitis. A diverticular bleed may be minor or cause hemodynamic compromise and potentially be life threatening. This argues for the adherence of a good bowel program to try and minimize the occurrence of these potential complications.

The superior mesenteric artery (SMA) syndrome has been reported in patients with neurological diseases. The syndrome occurs when the SMA that naturally crosses over the duodenum obstructs the duodenum, usually due to a more acute angle than usual. This can lead to dilatation of the proximal duodenum and stomach (39, 40). Multiple precipitating factors can be seen in TBI/SCI patients including weight loss, prolonged bed rest, loss of tone in the abdominal wall musculature and previous abdominal surgery.

Once SMA syndrome is considered, a radiological study is usually confirmatory. The diagnosis can be made by an upper GI series, computed abdominal tomography or rarely angiography. Management can include removal or reversal of a precipitating factor, nasogastric decompression as well as intravenous hydration. Occasionally, patients are tube feed for a short period of time while patients, who are very thin, gain weight.

## COMPLICATIONS OF BRAIN INJURY WITH NUTRITIONAL SIGNIFICANCE

Several other problems can be seen in patients with TBI that can have an impact on the patient's nutritional condition. These include the following: hyperglycemia, syndrome of inappropriate antidiuretic hormone (SIADH), cerebral salt wasting, seizures and the use of barbiturates.

### Hyperglycemia

TBI is associated with an acute sympathoadrenomedullary response characterized by increased blood levels of norepinephrine, epinephrine, and dopamine. Catecholamines levels reflect the severity of head injury and appear to predict the neurological outcome in both the acute and chronic phases of TBI. This increase in circulating catecholamines seems to contribute to intracranial hypertension, hyperdynamic cardiovascular response, increase in brain oxygen requirements, and the rise in serum glucose levels (41, 42). Rosner et al. showed that hyperglycemia occurred within minutes of experimental head injury in cats (43). In this animal model, hyperglycemia was related to severity of injury and was thought to be caused by catecholamine release. Similar results were also seen in rats (44). In another study in humans, Young et al. found that at the time of hospital admission 48% of 59 brain-injured patients had a blood glucose concentration  $>200$  mg/dL (45). Patients with peak 24-hour admission glucose greater than 200 mg/dL had worse neurologic outcome at 18 days, 3 months and 1 year than those with glucose levels less than or equal to 200 mg/dL. In a larger study of 169 patients who underwent surgery because of a traumatic intracranial hematoma, Lam and colleagues reported that glucose concentration at the time of hospital admission depended on the initial GCS (46). Patients with a best day-1 score of  $<8$  had an admission serum glucose of  $192 \pm 7$  mg/dL, compared with only  $130 \pm 8$  mg/dL in patients with a score of 12 to 15. Patients who subsequently remained in a vegetative state or died had significantly higher glucose levels both on admission and postoperatively than patients with good outcome or moderate disability. Among the more severely injured patients (GCS score  $<8$ ), a serum glucose level greater than 200 mg/dL postoperatively was associated with a significantly worse outcome ( $p < 0.01$ ) (46).

In summary, hyperglycemia is a common metabolic derangement seen early after both experimental and human TBI and is a significant predictor of poor outcome. It is thought that high glucose levels enhance ischemia-mediated cell damage, probably through lactate accumulation (47). When hyperglycemia is over 150 mg/dL, it is advisable to treat it with insulin. It has been shown that maintaining blood glucose at or below 110 mg/dL

reduces morbidity and mortality in critically ill patients in a surgical intensive care unit (48). However, more studies are needed to see if this can positively affect the neurologic outcome in patients with TBI.

### **Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH)**

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) should be suspected in any patient with TBI with hyponatremia ( $<135$  mEq/L), hypoosmolality ( $<280$  mOsm/L), a urine osmolality greater than that of plasma, a urine sodium concentration that is usually above 25 mEq/L, normal acid-base and potassium balance, and frequently a low plasma uric acid concentration. An inappropriate elevation in ADH release will produce hyponatremia by interfering with urinary dilution, thereby preventing the excretion of ingested water (49). In a review of 1808 patients with craniocerebral injuries, Doczi et al. reported that 84 patients (4.6%) developed SIADH. The prevalence varied depending on the severity of their head injury as follows: SIADH occurred in 0.6% of patients with mild head injury, 10.6% of those with moderate head injury, and 4.7% of the severe ones (II-10).

In another study of 109 patients with severe head injury with GCS  $<7$ , 33% of the patients had SIADH. The authors proposed to subdivide SIADH into two clinical forms: an early syndrome (5% of the patients) that becomes apparent towards the second day and is significantly associated with lesions at the base of the skull; and a delayed syndrome, which is more common occurring at the end of the first week where the cause could be due to different factors linked to intensive care procedures (51). Patients with this syndrome are generally responsive to fluid restriction, but this should be performed with extreme caution given the importance of maintaining normovolemia in patients with TBI (52). If serum sodium level falls below 140 mEq/L, the maintenance intravenous infusion should be changed to normal saline. For hyponatremia below 130 mEq/L, intravenous urea is safe and rapidly effective in correcting this problem. Urea is a potent osmotic diuretic and significantly increases sodium reabsorption at the kidney. The usual dose is forty grams of urea in 150 ml of normal saline, to be given over 2 hours and can be repeated every 8 hours. On average the serum sodium levels will rise 6 and 10 mEq/L after 24 and 48 hours of initiating therapy. Infusion of hypertonic saline is also effective, but generally takes longer than urea in correcting the hyponatremia and requires close monitoring of urine electrolytes (53). When tube feeding is done with patients with SIADH, formulas that are calorie dense (2 Kcal/cc) are generally used to limit the total volume delivered to the patient. Feeding tubes are then flushed with small amounts of normal saline rather than water.

### **Cerebral Salt Wasting (CSW)**

A less common syndrome than SIADH has been described in patients with brain injury (particularly subarachnoid hemorrhage) that mimics all of the findings in the SIADH, except that salt wasting is the primary defect with the ensuing volume depletion leading to a secondary rise in ADH release. The major distinction from SIADH is the volume status of the patient. In patients with CSW, the extracellular volume is contracted and the patient often appears dehydrated, whereas in SIADH a clinical picture of fluid overload is often seen. In addition to salt-wasting, affected patients also may have hypouricemia due to increased urinary uric acid excretion. The course of hypouricemia after therapy of hyponatremia may be helpful in distinguishing cerebral salt-wasting from SIADH. There is a suggestion that, after the correction of hyponatremia with fluid restriction, cerebral salt wasting is more likely to be present if hypouricemia continues in combination with an elevated fractional excretion of urate ( $>10$  percent) (49, 54).

The etiology of this putative syndrome is unclear. Preliminary studies supported the possible role of a circulating factor that impairs renal tubular function in many patients with intracranial disease. It had been proposed that a natriuretic hormone was released from the brain in response to certain types of injury; candidates included atrial natriuretic peptide, brain natriuretic peptide, and endogenous ouabain (55).

With the different pathogenesis, patients with CSW are treated differently from those with the SIADH. The objectives of the treatment are volume replacement and maintenance of a positive salt balance. Intravenous hydration with normal saline (0.9% NaCl), hypertonic saline (3% NaCl), or oral salt may be used alone or in combination, depending on the severity of hyponatremia and the ability of the patient to tolerate enteral administration. If the patient can tolerate oral intake, then 2–3 gm of NaCl are given 2–3 times daily or via a feeding tube, as appropriate. Volume status in response to treatment is best evaluated by daily weight and central venous pressure or pulmonary artery wedge pressure measurements (54, 56).

### **Seizures**

Three kinds of seizures can complicate the care of patients with severe brain injury, and these are distinguished by the time interval following trauma: 1) impact seizures, appearing within 24 hours; 2) early seizures, occurring within 1 week; and, 3) late seizures, observed from day 8 through to 2 years, but frequently later. The seizure type also varies with time period after brain injury, with a relatively high proportion of generalized seizures at an early stage and a progressively larger prevalence of partial seizures later (57, 58).

In a randomized trial of patients sustaining moderate or severe brain injuries, including patients with depressed skull fractures, Temkin and co-workers confirmed the effectiveness of prophylactic administration of phenytoin in significantly reducing the risk of seizures during the first week after injury (59). Routine administration of phenytoin for 7 days after sustaining a depressed skull fracture is supported by this study. In addition, other studies have shown that pharmacological control of early seizures with phenytoin, phenobarbital, valproic acid, and/or carbamazepine is effective. Anticonvulsants should be administered parenterally first, if possible, (phenobarbital 200 mg/day, phenytoin 500 to 750 mg/day, valproic acid 30 mg/kg/day, or carbamazepine 300 to 600 mg/day orally, since it is not available in intramuscular/intravenous formulations) and then switched to the oral route as soon as feasible. The enteral route is preferred due to cost and irritation to the veins from intravenous phenytoin. It should be noted that topiramate and valproic acid have been shown to cause diarrhea. Gastrointestinal function should be monitored, and treatment for diarrhea should be instituted to prevent skin breakdown for these patients (60, 61). Routine blood monitoring of anticonvulsant concentrations should also be performed when necessary for appropriate agents, and it is advisable to keep drug concentrations in the higher end of the therapeutic range (57, 62).

On the other hand, the efficacy of anticonvulsant therapy in reducing the incidence of late epilepsy remains unproven. Therefore, no acceptable effective prophylactic strategies are in place to inhibit late epileptogenesis following severe brain trauma. However, according to some authors, the decision to institute long-term prophylactic anticonvulsants can be justified in high-risk patients where the incidence of late seizures is over 20%. Such individuals would include those with the combination of post-traumatic amnesia of over 24 hours duration, seizures occurring during the first week after injury, and dural laceration or intracranial hematoma (63, 64).

It is important when providing nutrition for these sick patients at risk for post-traumatic seizures to look carefully at the factors that can lower their seizure threshold and try to address them promptly, and these include low anticonvulsant levels, electrolyte derangements (particularly low serum sodium, magnesium or calcium levels), hypoglycemia, hypoxemia, alcohol withdrawal and meningitis. It is important to recall that enteral feedings can decrease phenytoin availability by as much as 70%, and tube feedings should be held for 1 to 2 hours before and after phenytoin administration (65). This strategy has not always been effective, and serum levels of phenytoin are important to monitor. Increasing enteral doses of phenytoin may be required or even intravenous phenytoin to keep levels in the appropriate ranges (66, 67).

## Barbiturates

It is estimated that 10–15% of patients admitted with severe brain injury will ultimately manifest medically and surgically intractable elevated intracranial pressure (ICP) with an associated mortality of 84 to 100%. High dose barbiturates have been known since the 1930s to have ICP-lowering effects. However, their risks are well known, and complications have limited their applications to the most extreme of clinical situations (68). Barbiturates appear to exert their cerebral protective and ICP lowering effects through several distinct mechanisms: alterations in vascular tone, suppression of metabolism, and inhibition of free radical mediated lipid peroxidation. Pentobarbital is usually administered in an initial dose of 5 to 10 mg/Kg, given as a bolus dose of 50 mg initially, until the EEG shows burst suppression. Further intermittent intravenous doses can then be administered to maintain blood levels between 3.0 and 4.5 mg/dL. Pentobarbital usage is associated with a 20% decrease in the energy expenditure as measured by the Harris-Benedict equation (69).

Several studies showed that high dose barbiturate therapy was efficacious in lowering ICP and decreasing mortality in the setting of uncontrollable ICP refractory to all other conventional medical and surgical ICP-lowering treatments. When this therapy is used, consideration should be given to monitoring arteriovenous oxygen saturation as some patients may develop oligemic cerebral hypoxia (68, 70, 71). On the other hand, utilization of barbiturates for the prophylactic treatment of ICP was not shown to be effective and is not indicated. In a randomized controlled trial of 53 severely head-injured patients, Ward et al. showed no difference between the prophylactic barbiturate-induced coma group and the control, in the incidence of elevated ICP, the duration of ICP elevation, or the response of ICP elevations to treatment (72). Also, there were more complications seen in the treated group; arterial hypotension occurred in 14 patients (54%) in the treated group and only in two patients (7%) in the untreated group.

## GOALS OF NUTRITION THERAPY

The first important goal of nutrition therapy is to decrease the incidence of mortality associated with previously mentioned difficulties in feeding patients with TBI. These patients exhibit hypermetabolism, increased protein breakdown and turnover (73). Nutritional assessment is complicated by rapid volume shifts and fluid accumulation. Alterations in gut motility can also complicate the usual attempts to enterally feed patients.

Fortunately, most new patients with TBI/SCI are usually adequately nourished prior to their injury. The



complex physiologic response to injury creates difficulty in estimating calorie and protein needs, since these patients are often hypermetabolic (74). The hypermetabolic response can be prolonged and is usually inversely correlated with patient's GCS. Thus, the more severely brain-injured patients have a higher measured resting energy expenditure (MREE) (75). Caloric estimation is often calculated by the Harris-Benedict (HBE) equation; however, this formula has been shown to significantly underestimate energy expenditure in nearly 70% of critically ill patients (76). When available, indirect calorimetry is a better means of estimating the resting energy expenditure. Makk and colleagues showed that predictive formulas, like the HBE, could only correctly estimate the measured values obtained by indirect calorimetry in about 56% of traumatic brain injured patients (77).

It is commonly believed that the protein losses in patients with TBI come from immobility and the mobilization of protein to meet increased protein needs. However, data from trauma patients have shown that there is both increased protein synthesis and catabolism (78). The amount of nitrogen loss is associated with increased hormone levels that are associated with hypermetabolism, epinephrine, norepinephrine and glucagon (79). Immobility may exacerbate nitrogen losses, but steroid administration appears to have little effect (80). Trials that have attempted to correct negative nitrogen balance in the acute injury setting have had mixed results. Provision of high protein can help decrease nitrogen losses, but high nitrogen excretion is not eliminated by just simply increasing caloric intake (81). Recommendations for provision of protein in these patients will be discussed in more detail later. While patients are in critical condition in an Intensive Care Unit (ICU), it is more important to provide "some" nutrition rather than trying to meet 100% of a patient's estimated nutritional needs. Once out of the ICU setting, the nutritional focus should be to provide sufficient calories for growth and repair of body stores and proper weight attainment depending on the patient's functional capacity. The provision of protein is important to decrease the amount of cannibalization of muscles as a source of protein, since there is no distinct storage form for protein as there is for lipids, adipose tissue, or carbohydrate, glycogen in liver and muscle.

## NUTRITION ASSESSMENT AND REQUIREMENTS

Predicting the nutritional needs of a patient with TBI is not a simple task because no single test can predict nutrition status. In the recovery from a brain injury, nutrition status will not remain static, and therefore will require periodic reassessment and adjustments that are made depending on current weight and functional capability.

As most patients are either comatose or confused and unable to provide accurate information, family members or caregivers should be contacted as part of an initial subjective global assessment.

### Subjective Global Assessment

Subjective global assessment is well documented in the literature as a valid measure of nutritional status in hospitalized patients (82). It consists of 5 key areas from the medical history: 1) amount of weight loss over the previous six months; 2) usual dietary intake and if abnormal, length of time of abnormal intake; 3) gastrointestinal symptomatology (e.g, nausea, vomiting, diarrhea); 4) previous functional capacity (i.e., bedridden or independent); and, 5) metabolic demands of current disease state(s). A physical examination should also be completed to assess for muscle wasting, ascites, and edema. These factors should give an overall assessment of the patient's prior status and ability to utilize nutrients (82).

In response to brain injury, the systemic inflammatory process characterized by the previously discussed hormonal response, causes a shift from anabolism to catabolism (83). Hepatic glucose production leads to hyperglycemia in response to counterregulatory hormones. Despite exogenous insulin, resistance at the peripheral tissues makes glucose control difficult. Elevations in epinephrine and glucagon also increase lipolysis, which offers an additional fuel source. However, current data suggests that few lipids are oxidized and utilized for fuel (84). Therefore, protein is the major source of fuel following brain injury. Although the demand increases for acute-phase protein production by the liver, the liver is unable to keep up with urinary losses of nitrogen as protein is also used for gluconeogenesis. These losses contribute to further tissue breakdown and loss of muscle stores (83).

Severity of injury directly correlates with the degree of substrate mobilization. Therefore, the lower the GCS, the more significant the protein mobilization and calorie expenditure (85). Increased intracranial pressure is also associated with an increase in caloric expenditure (86).

In addition to severity of injury and intracranial pressure, motor activity, infection, fever, level of sedation, level of consciousness, and other trauma can also affect caloric expenditure. Ideally, indirect calorimetry is helpful in guiding nutritional care to assure adequate calories to allow protein synthesis and avoid overfeeding.

### Calculating Protein and Calorie Requirements

As indirect calorimetry may not always be available, several formulas have been published to estimate calorie needs. Estimated caloric requirements can vary from 140% to 200% above the normal. Studies have shown that this hypermetabolism can last from weeks up to one year post-injury (78). Current practice guidelines recommend to

provide 40–50 non-protein kcal/kg/day for patients with a GCS < 5 and 30–35 non-protein kcal/kg/day for patients with a GCS 8–12 (87, 88). As severe brain injury is correlated with significant stress, one must be prudent not to provide large amounts of carbohydrate as this may exacerbate hyperglycemia and potentially complicate ventilator weaning (89).

As many brain injuries do not occur in isolation, it is important to note if a spinal cord injury is present. As caloric expenditure decreases in correlation with the degree of muscle immobility, this will alter feeding regimens. Estimated caloric needs for spinal cord injury can be as low as 28 kcal/Kg for paraplegia and 23 kcal/kg for quadraplegia (78).

Despite adequate calories, excessive nitrogen losses have been noted in brain injury patients. Urinary nitrogen losses of up to 30 g/day have been documented in the acute course of injury. Nitrogen loss is well associated with epinephrine and glucagons levels (80). In addition, immobility can account for 25% of nitrogen losses (90).

Patients with TBI require 1.5–2 g of protein/Kg of usual body weight daily. Despite providing adequate calories and protein, positive nitrogen balance is often unachievable in the early weeks after injury and may be difficult to achieve until the patient stabilizes medically (88).

### Weight Loss Expectations

A secondary effect from hypermetabolism and hypercatabolism is weight loss. Loss of <10% of usual body weight is not considered significant. However, severe weight loss of up to 40% of usual body weight correlates with mortality. On average, patients lose  $15.6 \pm .9$  pounds during their acute hospitalization despite the provision of adequate nutrition support (75). If the patient also has a spinal cord injury, another 5–10% weight loss is expected due to muscle loss from immobility dependent on paraplegia or quadraplegia.

## ENTERAL VS. PARENTERAL NUTRITION SUPPORT

The use of enteral and parenteral nutrition has undergone significant changes over the past three decades. Initial fears about the use of hyperosmolar solutions in patients with TBI have been replaced with the aggressive use of TPN, but now attempts to use the GI tract as early as possible are commonplace.

### Gastric Feeding vs. Intestinal Feeding

The decision about what form of nutrition support to choose for a new patient with a TBI/SCI is an important one, and it should be addressed shortly after the initial injury. As previously shown, delays in providing nutrition

increase the risk of mortality or at least could prolong rehabilitation time (5). For patients with TBI, the main question will be if there is an associated abdominal injury that requires laparotomy? If so, then a surgeon may place a jejunal feeding tube at the time of surgery, thereby providing small bowel access. This concept has been popular at many trauma centers around the country, and more importantly, early enteral feeding may limit the progression to multiple organ failure (91–95). For isolated brain injury, facial fractures and spinal injury must be detected and stabilized before decisions regarding enteral nutrition can be made. These issues are important because they guide clinical decisions regarding the initial blind passage of nasoenteric tubes and the possible use of either radiologic or endoscopic enteral access options.

Although providing parenteral nutrition may be easier than obtaining adequate enteral access, enteral nutrition has a decreased incidence of complications and cost compared to parenteral nutrition with no significant differences in measured nutritional parameters (91,93). Also, provision of fuel substrates to the intestine can stimulate gut immune function and limit deterioration of the intestinal mucosa with bacterial translocation and its potential for contributing to sepsis (96, 97). It is known that attempts at bolus feeding (BF) in patients with TBI are associated with a high incidence of intolerance (98). It is believed that elevations in intracranial pressure delay gastric emptying. Also, BF can also be associated with gastric emptying delays. Recently, Rhoney and coworkers showed in a brain-injured population that continuous gastric feeding was significantly better tolerated than BF (99). Prokinetic agents were not found to be helpful, and medications such as propofol and sucralose were associated with feeding intolerance.

Klodell and colleagues showed that after early PEG placement that intragastric feeding was well tolerated in their patients with TBI. Five of the 118 patients did experience aspiration, but there was no evidence of intolerance prior to the aspiration (100).

In a related study, Neumann and DeLegge compared gastric versus small bowel feeding in an intensive care setting (101). They were also able to show that the gastric route was highly successful in feeding ICU patients without a marked increase in complications.

It is becoming clearer that attempts at enteral therapy should be made before using parenteral nutrition. Protocols for feeding should be developed for individual intensive care areas that stress the available resources for that unit. Careful attention must be made so that pulmonary aspiration is limited. Taylor et al. showed that enhanced enteral nutrition (started feeding rate at estimated needs the first day of feeding) appeared to enhance neurological recovery, as well as postinjury inflammatory responses and incidence of major complications (102).

Our group has shown that it is possible to obtain early enteral access in patients with TBI/SCI (103–106). Our

present protocol is to attempt gastric feeding, if it is deemed safe and feasible. Otherwise, endoscopic or fluoroscopic tube placement is performed as soon as it can be arranged. In this way, patients are fed as quickly as possible.

### **When to Use Parenteral Nutrition**

If the gut is nonfunctioning or safe enteral access cannot be achieved, then it is appropriate to fall back on the use of parenteral nutrition. Central venous access is necessary to infuse the hyperosmolar solutions, but the solutions are not dangerous, as previously believed. More importantly, it is crucial to be diligent over electrolyte changes and glucose levels. It is known that hyperglycemia over 220 mg/dl is associated with changes in the immune system so that attention to this detail is potentially critical in limiting infections associated with the use of parenteral nutrition (107).

Another common pitfall for the clinician is the concept that nutrition support must be "all or none." If the patient's nutritional needs cannot be met by enteral means alone, then it is acceptable to supplement this with intravenous nutrition to help approximate a patient's needs. Although overlap of enteral and parenteral nutrition is more common during the transition from parenteral to enteral therapy, there is no reason not to try to reach a patient's requirements by whatever combination yields results safely.

### **Choosing an Appropriate Formula**

Depending on calorie and protein needs, the clinician will need to utilize either a 1 kcal/cc high protein formula or a 2 kcal/cc formula. It has been our experience, that most 2 kcal/cc formulas do not meet estimated protein requirements for this population. Therefore, most patients will initially require use of a protein supplement to meet needs. A calorie dense formula may also be warranted in instances of fluid restriction for control of the syndrome of inappropriate antidiuretic hormone (SIADH).

The use of fiber must be considered in light of the medical plan of care. Fiber is avoided in cases where paralytics or pressors are being used as they may aggravate constipation from either reduced peristalsis or reduced gut perfusion. Once these medications are discontinued, fiber should be a part of the bowel regimen. This is especially important for patients with TBI that are likely to have long-term immobility or in patients with associated SCI.

### **Monitoring the Effectiveness of the Care Plan**

Daily assessment is critical in the intensive care unit to respond to changes in medical status. At a minimum, daily assessment should include an assessment of laboratory values, gastrointestinal function, tolerance to feedings, fluid balance, and medication changes. If intracranial pressure monitoring is present, it is helpful to

know how frequently it is drained as this may correlate with feeding tolerance. As feeding intolerance is noted, alternative recommendations should be noted. Weekly, a prealbumin and weight should be monitored for assessment of overall nutritional status.

Once medically stable and transferred to a non-intensive care unit, feeding tolerance should be monitored daily. Laboratory values may be checked more infrequently as long as not medically indicated, and the patient continues to tolerate feedings. Weights and prealbumins remain important indicators in this population to monitor overall status and needs. As time progresses, a patient's metabolism may slow, requiring a change in feeding regimen in order to achieve weight maintenance or loss. Prealbumin is useful in determining if calories and protein intake are adequate to prevent skin breakdown, while continuing to decrease overall calories. Feedback from physical and occupational therapists regarding mobility and skin breakdown is also helpful in estimating ongoing calorie and protein needs.

### **Micronutrient Supplementation**

Vitamins and minerals should be supplemented if feeding volumes or oral intake does not meet the recommended dietary allowances. Antioxidants are felt to play a protective role in the recovery after brain injury. No significant changes in vitamin E levels have been observed in a recent study after brain injury. Therefore, it is felt that there is no benefit for additional supplementation (108).

Ascorbic acid is also known for its antioxidant properties. Polidori and coworkers demonstrated that ascorbic acid levels decreased during the first week after brain injury likely as a result of oxidative stress. These levels were inversely related to the GCS score and the major diameter of the lesion. Further studies are needed to see if vitamin C supplementation would be beneficial (109).

Zinc deficiency has been observed on admission and through the first two weeks of hospitalization (110). Adequate zinc status is necessary to minimize neuroimmune cell death in animal models. In addition, zinc supplementation has been utilized to treat deficiency and the severe protein turnover in patients with TBI (111). Daily supplementation of 12 mg of zinc is recommended (112). Losses can be substantial if patients have diarrhea or associated traumatic injury with enterocutaneous fistulas that drain significant amounts of fluid.

## **IMMUNE ENHANCING NUTRITIONAL SUPPORT ISSUES**

### **The Role of Arginine**

Arginine is a conditionally essential amino acid. Under normal circumstances it is synthesized endogenously from

L-citrulline. However, during stressful periods such as growth, illness, or metabolic stress, endogenous synthesis is unable to meet the increasing body demands, and a dietary source is required. On administration of pharmacologic doses, arginine stimulates the pituitary growth hormone, insulin-like growth factor, prolactin, insulin and other hormones, resulting in net positive effect on wound healing and immune functions (113). It is also a precursor for growth substances like putrescine, spermine, and spermidine. Importantly, arginine is a precursor for nitrates, nitrites, and nitric oxide. Nitric oxide is particularly important as a vasodilator, but it also participates in immunologic reactions, including the ability of macrophages to kill tumor cells and bacteria. These and other functions of arginine are still being evaluated, but it is clear that supplementation of arginine can have a generally positive effect on immune system functions and wound healing in humans and animal (114,115). Numerous studies have demonstrated suppression of T-cell mediated immune function after major surgery or trauma. Daly et al. studied the effect of 30 g per day of arginine on patients undergoing elective surgeries compared to an isonitrogenous placebo (116). T-cell mediated immune function was evaluated preoperatively and 1, 4, and 7 days postoperatively. Patients who received arginine demonstrated a quicker return to normal T-cell function measured by *in vitro* mitogen proliferation assays. This study also revealed increases in the CD<sub>4</sub> phenotype, which further suggests that supplemental level of arginine helps T-cell levels to recover faster (116).

### The Role of Glutamine

Glutamine is also considered a conditionally essential amino acid. Of interest, it is the most abundant amino acid in the body. One of glutamine's major roles is as an oxidative fuel for rapidly replicating cells including gastrointestinal mucosal cells, enterocytes and colonocytes, as well as immune cells, lymphocytes and macrophages (113). Furthermore, glutamine appears to convey a protective or restorative influence on the GI tract, which may decrease translocation of enteric bacteria across the mucosal barrier. Perhaps the most compelling evidence for the immunomodulatory effects of glutamine comes from Ziegler et al. who studied 45 bone marrow transplant patients receiving either TPN supplemented with glutamine or an isonitrogenous, isocaloric control. Patients who received glutamine in their TPN demonstrated decreased incidence of infection and shorter hospital stay compared to the control group (117).

Unfortunately, the chemical structure of glutamine is relatively unstable in solution, unless the glutamine is bound to protein. Until recently, enteral formulas supplemented with glutamine were available only in powder form. Also, new technology using glutamine

hydrolysate formulas and glutamine dipeptide has led to the development of high glutamine liquid formulas that are compatible with TPN. It is important to note that there are no studies available that currently assess the direct effect of either glutamine or arginine in patients with TBI.

### Are Immune Enhancing Formulas Indicated in This Population?

There is sparse information available discussing immune enhancing diets and brain injury. The first study was published in abstract form, patients with severe closed head injury defined as GCS <8 with evidence of brain injury on imaging were randomized to an immune-modulated diet rich in glutamine, arginine, fish oil and nucleotides (11 patients), Impact (Novartis Nutrition, Minneapolis, MN) or standard diet (9 patients), both via feeding tube (118). Patients were followed prospectively up to one week. In their findings, the infection rate was significantly lower in the enhanced diet group (9.1% vs 100%,  $p < 0.0001$ ), also there was significant improvement in the total lymphocyte count and percent of CD<sub>4</sub> count in the study group (118). However, this study generated several areas of concerns as follows: the study is only available in abstract form, and also the sample size was too small to provide significant statistical analysis. The next paper addressing the use of immune enhancing formulas compared two immune diets; Crucial (Nestle Nutrition, Deerfield, IL) and Impact (119). This study involved multiple trauma patients, but 9 of 13 patients had severe closed head injury. This prospective study consisted of 13 patients randomized to receive enterally either Crucial or Impact. The randomized diet was given for seven days with study measurements obtained at study entry and day 7. The feedings goals were calculated based on protein delivery of 1.5 g/Kg body weight. Feedings were started at 30 ml per hour and advanced 20 ml per hour every 4 to 8 hours until goal was met. The exact study conclusion was very difficult to interpret. The authors concluded that patients receiving Crucial had normalization of IL-1 release from peripheral monocytes incubated with lipopolysaccharide (LPS) *in vitro*, but no alteration was noted with Impact (119). This limited study did not lead to any concrete conclusions regarding these diets in patients with TBI.

The most recent study dealing with immune enhancing diets in head injury compared early enteral feeding to late enteral feeding with Impact in a prospective, randomized fashion. The early group received enteral feeding <72 hours after admission and the late group received feeding upon resolution of the ileus from their head injury. The overall conclusion was that there was no significant difference between the two studied groups, but there was trend for higher mortality in the late group (4 of 15) (120).

Based on the available studies, very few conclusions on the use of immune modulated formulas in patients with TBI can be made. The single best conclusion is that these diets seem to be well tolerated. Further clinical investigations are needed in this area, involving larger number of patients, to be studied in a randomized, prospective blinded way, comparing the immune enhancing diets to an isonitrogenous control.

## REHABILITATION ISSUES

Once the patient stabilizes and transfers to the rehabilitation service, the team's goals are to normalize the patient's care in a safe environment and provide education for post-discharge placement. The major nutritional issues are dysphagia, maintaining a realistic body weight, and bowel regimens.

### Dysphagia

The treatment of dysphagia requires a team effort between the speech-language pathologists, physiatrist, nursing staff, and dietitian. The overall goal is to find the least restrictive diet that promotes safe swallowing and maintains nutritional status. Patients who have been found to be at the highest risk for oropharyngeal dysphagia include the following: those with an admitting GCS of 3–5, a Ranchos Los Amigos Scale of Cognitive Functioning at Level II, a CT scan which demonstrated midline shift or brain pathology requiring an emergency craniotomy, or ventilation time greater than or equal to 15 days (121). Patients who remain lethargic and have a GCS less than 12 should not be considered for oral intake without a swallowing evaluation.

Typical swallowing disorders include oral preparatory problems, oral transit disorders, delayed pharyngeal swallow and pharyngeal neuromuscular abnormalities. A modified barium swallow or flexible endoscopic evaluation of a swallow are two useful tests to identify safe consistencies for oral intake and patients at risk for silent aspiration (122).

In addition to evaluating a functional swallow, patients must be assessed for readiness to feed. Barriers to feeding include cognitive and motor planning behaviors, such as impulsivity, distractibility, inability to stay on task, poor sequencing skills, lack of initiation, and inability to motor plan self-feeding. For patients exhibiting these behaviors it is imperative to provide an environment for feeding that is free of distractions and yet can provide a safe level of supervision and assistance (123). For further review of dysphagia issues, please refer to Chapter 47 entitled "Evaluation and Treatment of Swallowing Problems After TBI."

The National Dysphagia Diet was instituted in April 2002 to standardize food consistencies and terminology throughout the health care continuum. Liquids can be

given as thin, nectar-like, honey-like, and spoon-thick. Of concern, is that the thicker the liquid is made, the less fluid is usually consumed by the patient. Many of these patients will require an additional source for hydration either by intravenous fluids or by a feeding tube (124).

Solid food consistency can be determined by the speech language pathologist. These textures may vary from a blended smooth texture (called pureed), to a ground moist consistency (called mechanically altered), to a general diet. Dry foods are generally eliminated as they are difficult to maneuver in the oral phase with decreased tongue movement and/or difficult to propel with disco-ordination in the pharyngeal phase of the swallow.

Once a patient is advanced to oral intake, nutrition support regimens should be reevaluated. A dietitian is helpful in evaluating adequacy of oral intake and assisting in making recommendations for the weaning of nutrition support. Feeding schedules should either be nocturnal or after a meal to encourage oral intake. Calorie counts are often useful in weaning a patient from tube feeding. According to the Nutrition Practice Guidelines for Dysphagia of the American Dietetic Association, tube feedings should be discontinued when patients can consume 80% or greater of their estimated nutritional needs consistently.

### Maintenance of Realistic Body Weight

The hypercatabolism of brain injury that drives weight loss generally stops and plateaus at three months post-injury. Information regarding mobility and progress in therapies and activities of daily living are useful in reassessing calorie needs. The more muscle groups utilized, the more muscle that is spared from disuse (125). Many patients have increased calorie needs during rehabilitation due to the calories spent during the work process of therapy. This increase can be 30–60% higher than control groups. Assistive devices can ease this increase (126).

Weekly weights are very useful in monitoring for weight gain or loss. As medical status normalizes, calorie demands decrease. Of utmost importance for patients and their families is to realize that if they have limited mobility or paresis, calorie needs are likely lower than normal. Indirect calorimetry was performed on non-ambulatory tube fed adults with neurologic disabilities. This study demonstrated an approximate 25% decrease in caloric needs for patients with fixed upper extremity contractures (127). Weight gain is also the result of altered food intake patterns. Some patients experience hyperphagia, which is compounded by a poor memory of when they last ate. Brain injured patients are noted to consume larger meals and more calories per day than controls. This occurs without regard to pre-meal stomach contents. Also, social factors are not an indicator of meal size (128).

These are important considerations in regards to planning a diet for weight loss or weight maintenance.

Behavior strategies should be employed that will limit access to food and get individuals into a set schedule of eating. Memory boards or diaries may be helpful in reminding individuals of the time and content of their last meal. Individuals should be discouraged from automatically eating because they think they are hungry.

Patients should be encouraged to follow a low-fat well-balanced diet. The food guide pyramid is a starting resource for diet planning. In addition, they should consult a registered dietitian or recognized weight management center (e.g. Weight Watchers) for assistance with individualized dietary meal plans. A registered dietitian can also provide the caregivers' support and assist in monitoring the effectiveness of the weight loss plan.

Obesity and decreased mobility can precipitate pressure sore development in the chronic care setting (129, 130). Therefore, all brain injury patients with limited mobility should receive periodic routine skin assessments. If skin breakdown is noted, a further nutritional assessment is warranted.

Malnutrition can delay wound healing. It is important that deficiencies of protein, vitamins and minerals be replenished to allow for tissue growth and repair. Frequently, a deficiency is not clinically noted; however, it has become practice to provide daily supplementation of vitamins (131, 132). In patients without significant liver or renal disease, a daily multivitamin and an additional 500 mg of ascorbic acid are recommended. Vitamin A and zinc should also be given if pressure sores do not heal or progress in staging (133). Clinicians should review dietary habits with patients to also ensure adequate calories and increased protein for wound healing (134).

### Bowel Regimens

For non-ambulatory patients and especially those with a spinal cord injury, bowel programs are an essential part of their medical management. The chronic patient should eat a high fiber diet of at least 30 grams per day. Good sources of fiber include whole grains, bran products, leafy greens and raw vegetables (135).

### WITHDRAWAL OF FEEDINGS

It is beyond the scope of this chapter to delve in to all of the medical, legal, religious, and emotional issues that concern the potential withdrawal of nutrition support. Many states in the U.S. as well as many countries worldwide deal with end of life issues differently. Most importantly we, as health care professionals, must be advocates for the patient who may not be able to voice an opinion, and we must seek guidance as to their possible wishes from family and/or other loved ones.

### CONCLUSIONS

Care of patients with TBI can be complex, yet rewarding. The gastrointestinal and nutritional ramifications of an individual's disease may be straightforward or require a specialist's input. Time should be taken to review the potential needs of each patient and care plans should be created and implemented. Further understanding of the underlying disease will improve the delivery of comprehensive care to these afflicted patients. The next few decades will likely see marked advances in both.

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# 37

## Sexuality, Reproduction, and Neuroendocrine Disorders Following TBI

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### INTRODUCTION

Our understanding of human sexuality has evolved over the last century to a greater appreciation of the biological, cultural and psychological factors that underpin sexual behavior. Freud's groundbreaking and controversial theories on psychosexual development and sexuality were based on the understanding that sexuality is a primary component of human development and functioning. Although some of Freud's beliefs about sexual development have been questioned, his understanding of the importance of sexuality in human life has been an important contribution to medicine, science, and the social sciences.

Biologists and ethnologists have studied animal models of sexual physiology and functioning, and these models have been important in advancing our understanding of human sexual behavior. These approaches have informed us that there is a wide range of variability in the expression of sexual and reproductive behaviors across species. In addition, anatomists and physiologists have further advanced our understanding of human reproduction and human sexuality.

Social and cultural beliefs have also contributed to our evolving understanding of sexual behavior. Sociologists and anthropologists have studied broad variations in human behavior across cultures. Behaviors considered deviant in one culture might be accepted practices in another. Gender, sex roles, and sexual orientation are

prime examples of differences that may be heavily influenced by cultural and political forces. Human sexual behavior is based upon a complex interaction of biological, psychological, and cultural factors. Unfortunately, most of sexology research over the last few decades has focused on males and on heterosexual populations, although this bias is gradually being recognized and funding of research in the area has been more comprehensive in recent years. Research focused on women with traumatic brain injury is also sparse (1).

A traumatic brain injury (TBI) profoundly affects every aspect of an individual's functioning. These injuries have an impact on physical, cognitive, emotional, behavioral, and social functioning. Physical disabilities may be caused by anatomic or physiologic changes as a result of the injury. Cognitive disabilities commonly include problems with concentration, learning, memory, information processing, language, problem-solving, reasoning, planning, and organizational skills. Emotional difficulties are not only limited to psychological disorders such as depression, but also difficulties that affect behavior and personality. Behavioral problems can include impulsivity, poor initiation, perseverative behaviors, and other frontal lobe disturbances. Interpersonal skills problems may significantly influence social and occupational functioning. The complexity of all of these factors and their interrelationships creates a number of methodological challenges for research in the area of sexuality and TBI.

## SEXUAL RESPONSE MODELS AND SEXUAL DYSFUNCTION

According to the Masters and Johnson model of the 1960's, the sexual response cycle consists of four phases: excitement, plateau, orgasm, and resolution (2). A simplified model, described by Kaplan (3), included only desire, excitement, and orgasm. More recently described models take into account new perspectives and new research, suggesting that the genital focus of previous models and the linear sequence inherent to these models inaccurately reflects the cyclical nature of the interactions within the mind and between the mind and body during intimacy and sexual activity. Sexuality for women, and also for men, includes an interaction of personal factors such as self-image and desire for connection, but must also be seen within the context of family, interpersonal relationships, society and culture. Life stressors, including financial and health issues, also contribute to the sexual and intimate interactions between couples (4, 5).

An alternative sexual response cycle model described by Basson (6) takes into account other aspects of sexuality and intimacy: the desire to express affection and to share pleasure, a sense of being attracted to and attractive to another, and a sense of commitment. This model emphasizes that sexual experiences may begin with a non-sexual state of mind, and take place within a much larger context of cognition and behavior, acknowledging the importance of the aspects of intimacy that contribute to both the non-sexual and the sexual state of mind. These factors include communication, respect, trust, vulnerability, and fear of loss.

### Definitions of Sexual Dysfunction

Sexual desire disorders include sexual aversion and hypoactive sexual desire. Sexual arousal disorders result in poor lubrication in women and erectile disorders in both men (penile) and women (clitoral). Orgasmic disorders include anorgasmia in men and women and premature ejaculation in men. Sexual pain disorders include dyspareunia and vaginismus. An international consensus development conference on female sexual dysfunction resulted in an expansion of these classifications.

The existing classification system for sexual dysfunction, based on the World Health Organization (WHO) International Classification of Disease-10 (7) and the Diagnostic and Statistical Manual of Mental Disorders (8), has been challenged by an interdisciplinary consensus conference panel, consisting of 19 experts in female sexual dysfunction. The former classifications were expanded to include psychogenic and organic causes of desire, arousal, orgasm, and sexual pain disorders. A personal distress criterion has been added; this criterion specifies that a condition is considered a disorder only if

it creates distress for the woman experiencing the condition. As noted by Sipski (9), patients with traumatic brain injuries may lack awareness and appreciation of "personal distress." Definitions of sexual arousal and hypoactive sexual desire disorders were developed in this new classification system, and a category of noncoital sexual pain disorder was added (10).

Many psychological and biological factors influence the processing of sexual, sensual, or erotic stimuli. Psychological factors include past experiences (positive, affirming, negative, or traumatizing) and responses to the present sexual context. Inadequate or impaired emotional development may also influence openness to sexual experience, and result in lack of sexual arousal or even dysphoric arousal. Emotional intimacy and physical satisfaction with the sexual experience may not necessarily include orgasmic release. Biological factors that affect the processing of sexual stimuli include depression, medications that impair sexual function, fatigue, sleep disturbance, substance use, other medical conditions, and neuroendocrine factors.

Individuals may also experience anxiety about intimacy, sexual performance, or consequences of sexual activity. This anxiety may be a primary or secondary factor in the development of sexual dysfunction. Anxiety may interfere with any stage of the sexual response cycle and commonly plays a role in arousal conditions such as premature ejaculation, erectile dysfunction, and arousal dysfunction in women.

Studies suggest that sexual dysfunction is more prevalent in women than in men in the United States and a number of other countries. Prevalence data is dependent on the assessment techniques, which are variable (4). The Massachusetts Women's Health Study (11,12) documented decreased sexual desire among married women, those with psychological symptoms, cigarette smokers, and those in the perimenopausal state. However, of note, in healthy women, the prevalence of sexual dysfunction actually appears to decline with age, and frequency of sexual intercourse is not related to menopausal status. (11-13)

There may be differences in sexual desire and drive between men and women, although this is still an area of considerable controversy (14). Male sex drive may be more urgent, less distractible, more goal-oriented, and more focused on intercourse; female sex drive may be more diffuse, more distractible, more receptive, and more motivated by a desire for affection and emotional connection. Female desire may be more contextual, more aroused by words than images, more emotional than biological, more sensual than genital, more flexible and mutable. Men report more sexual fantasies and thoughts and experience more spontaneous sexual desire, report having more desire for more sexual partners, masturbate at younger ages and with greater frequency, and become aware of their sexual drive earlier than women. Men also

show a greater preference for sexual variety and novelty, have more favorable attitudes towards their genitals, and report higher and more consistent levels of desire across their lifetime (15, 16). To what extent these differences are culturally driven, or influenced by societal roles, teachings and expectations, is poorly understood (14–16).

Most studies of sexuality to date have focused on heterosexual populations. The research related to sexuality within gay, lesbian, and transgender populations suggests that even more complexity is inherent in the study of human sexuality than has been formerly appreciated. As these topics are discussed and researched more widely, our understanding of human sexuality is evolving towards a greater awareness of how societal and cultural influences shape the understanding and expression of sexuality. This may in fact lead to more openness, acceptance, diversity of expression, and greater sexual health for all.

## NEUROLOGICAL SYSTEMS AND SEXUALITY

The neurological aspects of sexuality include widespread and complex relationships among the neuroanatomic, neurochemical, neurophysiological, and neuropsychological systems that govern behavior, including what we define as emotional, physical, sensory, and cognitive components. The resulting sexual behaviors can be described more concretely as motivation, desire, arousal, genital responses, and orgasm.

Our understanding of the brain-behavior relationships that are the basis for human sexuality is primarily derived from animal studies, and therefore our conclusions must be tentative. The inter-relationships among the systems that contribute to these concrete behaviors are not completely understood. However, the peripheral nervous system, including motor, sensory and autonomic neurons, and subcortical and cortical systems, contribute to sexual interest and responsiveness through an elaborate network. Lesions at any level may influence this behavior, although the actual effects of such lesions in humans are not fully established. Central nervous system control of sexual function is similarly organized in men and women (17).

### Chemical Messengers

Neurotransmitters play a critical role in the physiological basis of sexual behaviors and sexual response. Spinal cord centers are under the control of brain regions that exert both excitatory and inhibitory influences. Sexual desire has been linked to activity of dopaminergic systems, including the mesolimbic and mesocortical systems. Serotonin may have an inhibiting effect on sexual function. Hypothalamic spinal pathways using oxytocin as a neurotransmitter have also been identified. Nitric oxide, crucial for sexual function at the genital level, may also

be an important central nervous system messenger. Receptors for gonadal hormones include neurons in the midbrain, hypothalamus, and amygdala. The supraspinal sites involved in the sexual response network have both extensive interconnections and receive genital sensory input. There does not appear to be a strict division between reflexive and psychogenic responses given this organizational structure (17).

### Spinal Systems

A coordinated system of sympathetic, parasympathetic, and somatic spinal outflow tracts are the basis for human sexual response. The spinal cord is “necessary and sufficient” to produce sexual responsiveness (17). Genital innervation is somatic as well as autonomic (i.e., parasympathetic and sympathetic). Somatic sensory afferents, synapsing in the sacral spinal cord, induce local sexual responses and project sensory information to cortical regions, resulting in sexual awareness and sexual excitation. Parasympathetic innervation originating at the sacral level, organized in the pelvic nerves, supply the neuronal inputs and outputs responsible for the initiation and maintenance of the erectile response. Erections are observed after lesions of sacral cord segments and pelvic nerves and the psychogenic erections in paraplegics with conus or cauda equina lesions may occur because of other non-cerebral proerectile pathways operating via the hypogastric nerves (18). Psychogenic mechanisms of arousal may also be transmitted in sympathetic pathways. Sympathetic neurons from the thoracic cord, contained in the hypogastric plexus, provide efferent and afferent innervations to the internal genitalia; this system provides the neurological basis for emission. Ejaculation is a result of sympathetic outflow from T11-L2 segments including the sympathetic chain, the hypogastric plexus, and pelvic and pudendal nerve systems (19).

In women, these neurological connections are also the basis for sexual responses, including arousal, lubrication, and female ejaculation. Parasympathetic activity causes clitoral erection, engorgement of the labia, and vaginal lubrication. Orgasmic sympathetic activity results in contraction of pelvic structures including uterus, fallopian tubes, paraurethral glands, and pelvic floor muscles (20).

### The Brainstem and Related Structures

Brainstem centers that contribute to human sexual responses include the reticular activating systems of the pons and midbrain. These pathways, which provide input for initiation and maintenance of arousal and alertness, connect with limbic and other frontal structures, many of which play a role in sexual and sexually related behaviors, including affective responses. Brainstem regions connect with diencephalic structures and limbic and paralimbic structures including the hippocampus, septal

complex, cingulate gyrus, amygdala, and hypothalamus. Stimulation of these structures produces erection, and in some cases pre-orgasmic sensations of pleasure. Lesions of the piriform cortex, which is inter-connected with the olfactory cortex, produce hypersexual responses in animals. The role of the basal ganglia in sexual function is not clear, although stimulation may result in species-specific sexual behaviors (21).

### Subcortical Systems

The primary areas of the hypothalamus that contribute to sexual response are the paraventricular nucleus, tuberal region, medial preoptic area, and the dorsal hypothalamic area. These hypothalamic regions are likely involved in both sexual desire and sexual response. The basal hypothalamus is influenced by tissue levels of testosterone, dihydrotestosterone, and estradiol. The preoptic area has high concentrations of androgen and estrogen receptors, and the enzyme that converts androgens to estrogens. Manipulating androgens and androgen receptors in this region affects sexual behavior. Lesions in the medial preoptic area of the hypothalamus reduce or eliminate sexual behavior. This area receives neuronal inputs from other brain regions such as the olfactory system and the cerebral cortex, including the visual cortex (17, 19, 22).

The dorsomedial nucleus of the hypothalamus, when stimulated, produces ejaculation. This nucleus may receive input from the medial preoptic area and probably from other brain and body regions. The ventromedial nucleus of the hypothalamus appears to play a role in female sexual behaviors. This nucleus is also strongly influenced by sex hormones, in particular estrogen and progesterone. The hypothalamus receives some of its information in the form of neuronal messages, but other information arrives in the form of chemical messages, including gonadal steroids. In addition, the hypothalamus synthesizes and secretes hormones of its own, many of which exert influences over sex and reproduction (22).

The pituitary hormones play a crucial role in the sexual and reproductive activity of humans. Gonadotropin-releasing hormone stimulates the release of follicle-stimulation hormone (FSH) and luteinizing hormone (LH) regulates the menstrual cycle in women and testosterone secretion in men. Males with hypothalamo-pituitary disorders have decreased or absent sexual desire, and often this is the first symptom to appear. In females with hypothalamo-pituitary disorders, two-thirds notice absence or a considerable decrease in sexual desire; lubrication and anorgasmia are also very common (23).

### Cortical Systems

The Kluver-Bucy syndrome results from injury or ablation to the anterior temporal poles, and the syndrome

includes hypersexual and exploratory behaviors, and hyperorality (24, 25). Temporal lobe seizures may be manifested by genital sensation and other sexual phenomena, with hypersexual or hyposexual behavior during both ictal and interictal periods. Endocrine disturbances, which are common in both men and women with temporal lobe epilepsy, result in decreased libido, impotence, menstrual disturbances, and reproductive disorders (26–28).

The frontal lobes are clearly involved in the regulation of sexual behaviors. Injury to the orbitofrontal regions (limbic and paralimbic lesions) may produce hypersexual responses. Socially inappropriate behaviors are displayed more often than sexual behaviors. In the case of dorsolateral frontal injury, when attention and initiation impairments are primary, libido or sexual assertiveness may be impaired (29). Injury to these areas may also lead to an inability to fantasize (30). The role of the olfactory system is unclear, but recent research indicates that anosmia may not significantly affect sexual function. The hypothalamus is a crucial structure in the elaboration of the human sexual response. The supraoptic nucleus of the hypothalamus synthesizes oxytocin, a hormone involved in lactation, birthing, and orgasm. Naloxone, an opiate antagonist, prevents the release of oxytocin, suggesting that the release at orgasm is controlled, at least in part, by the endorphin system (31, 32).

## SEXUAL DYSFUNCTION AFTER BRAIN INJURY

For the person with a disabling disease, condition, or injury, questions of sexuality are complex. Because of multiple, interrelated impairments that coexist after traumatic brain injury, questions concerning the specific etiologies of sexual dysfunction remain unanswered. How do we understand the impact of the pathophysiologic processes on the individual? What alterations in sexual desire, drive, arousal, or sexual responses are due to organic factors, and what can be attributed to secondary factors, such as cognitive, emotional, behavioral, and communication impairments or mobility deficits that result from the disease, condition, or injury?

Although much of the literature about TBI focuses on psychosocial consequences, no well-designed studies have established clear links between both the various impairments that frequently occur and the sexual dysfunction. Are impairments such as communication or cognitive deficits more important in interpersonal relationships than physical deficits? What roles do depression or other psychological conditions play? What are the effects of medication? What interpersonal and relationship issues contribute to sexual dysfunction? What are the anatomic correlates of sexual dysfunction?

The impact of TBI on relationships within the family and on mood and affective states of significant others and spouses has been explored in a large number of studies both in the United States and abroad. Thomsen's study (33) of 50 severely injured Danish patients demonstrated that family members were more disturbed by intellectual than physical deficits. The relationships were better between single adult patients and mothers than between patients and spouses. In Rosenbaum and Najenson's study (34) of brain-injured veterans in Israel, wives endorsed with high frequency the statement "dislikes physical contact with husband." The spouse's mood was associated with decreased levels of sexual activity. Lezak (35) emphasized that emotional adjustment for family members, including spouses, occurred only after detachment and acceptance of the permanence of deficits. This adjustment culminated in divorce, separation, and long-term placements for some partners. Bond (36) noted that the level of sexual activity among partners was not related to severity as measured by the duration of post-traumatic amnesia or level of cognitive or physical impairment.

Sexual function and marital adjustment were studied in a small group of married couples (37). Frequency of intercourse declined for all couples, but to a greater degree for couples in which the husband was brain-injured; orgasm in female spouses also showed a significant decline. Kreuter and associates (38) examined quality of relationships in 92 persons with TBI from 1 to 20 years post injury. They found that 58% had a stable partner relationship at the time of the study and of these 55% were established after the injury. In a larger study, sexual functioning, mood, and quality of life were examined in 322 individuals with TBI and a non-TBI sample of 264 individuals without disability (39). This study found that men with TBI were less sexually active and fewer were involved in a relationship when compared with non-disabled controls. Interestingly, there were no significant differences between women with and without TBI on these same variables.

Kreuter, Dahloff and associates (40) also examined sexual adjustment following TBI. In a group of subjects who were sexually active prior to their injury, 30% of the men experienced erectile dysfunction and fewer ejaculations. Although 59% reported no changes in orgasm, 40% experienced orgasm difficulties. "Dissatisfaction with the frequency of sexual activity" was found in 56% of the subjects. This study found that approximately one third of respondents had no intimate partner following the injury. However, they found that sexual dissatisfaction in individuals with partners was related to decreased interest, low self-esteem, partners' decreased interest (willingness to engage in sexual activity), "physical unattractiveness," and decreased sexual ability.

Kosteljanetz and associates (41) noted a correlation between intellectual impairment and sexual dysfunction in

a group of 19 mildly injured patients. Although some studies (34) indicate no relationship between locus of lesion and sexual dysfunction, medial basal-frontal injury or diencephalic injury was associated with hypersexuality and limbic injury with changes in sexual orientation in a population of 8 patients (42) Kreutzer and Zasler (43) studied a population of 21 brain-injured men and noted declines in sex drive, erectile function, and frequency of intercourse. Although one third of the married subjects reported their relationship as worse post-injury, 40% rated their relationships as good or very good when compared to their pre-injury relationship status. The authors found no correlation between affect and sexual behavior.

Although Zasler (44) found no association between affect and sexual dysfunction, a larger study (45) using measures of anxiety and depression for both partners found a significant level of psychiatric dysfunction. In addition, as time since injury increased, males with TBI became more sexually dissatisfied and sexual communication became more problematic for their partners. Age and time since injury were related to measures of psychosexual dysfunction, but severity of injury was not. TBI subjects in another study reported significant levels of anxiety and depression and found significant correlations between sexual adjustment and measures of psychosocial adjustment (38, 40).

The negative impact of pre-injury and/or post-injury substance use on physical, cognitive, and psychosocial functioning is clearly documented in the literature. The rates of pre-injury and post-injury substance abuse in individuals with TBI are substantial. Approximately 16% to 66% have chronic pre-injury problem drinking and 10% to 50% continue to experience post-injury problems with alcohol (46–48). Problems include a higher incidence of medical and psychological complications during TBI recovery, poorer cognitive recovery, poorer long-term outcome, and exacerbation of cognitive and behavioral deficits. Most substances of abuse have been shown to adversely affect sexual functioning at some stage in the sexual response cycle in non-TBI subjects, and have a substantial negative impact on sexual functioning in individuals with TBI who use substances (49).

Given that most injuries occur in individuals between the ages of 15 and 25, limitations in the person's pre-injury sexual experience can influence post-injury sexual functioning. Individuals with limited sexual experience and knowledge often have significant deficits and experience in establishing and maintaining intimate relationships. These relationship deficits can greatly reduce their ability to meet people who may become potential intimate partners. In individuals who have an intimate relationship at the time of injury, cognitive, emotional, behavioral, physical impairments, and substance abuse post-injury can clearly have a negative effect on the quality of the relationship as well as the sexual functioning

of partners. For individuals who have limited relationship skills prior to their injury, these problems are amplified.

The impact of TBI on the sexual response cycle has also been closely examined. In general, problems may occur at any stage (desire, excitement or arousal, orgasm, and resolution). Sexual difficulties are found in a number of areas including decreased frequency of intercourse, decreased desire, impaired arousal, and orgasmic dysfunction (40,41,45) Aloni and Katz (50) reviewed the existing literature on the effects of TBI and the sexual response cycle. Although significantly more individuals with TBI experience decreased desire, some report increased desire. Kreuter et al. (40) examined 65 men and 27 women with TBI and found decreased desire, erectile dysfunction, and orgasmic dysfunction in many of their subjects. However, 59% of their sample reported no change in orgasm post-injury and 50% noted no change in frequency of sexual intercourse post-injury.

A study by Sandel and associates (51) examined sexual functioning in a group of male and female outpatients with severe traumatic brain injuries (average length of post-traumatic amnesia was 54 days). Sexual function was consistently lower than in the normal population but significantly only on the (1) orgasm and (2) drive and desire subscales of the Derogatis Interview of Sexual Function (52). Location of injury was relevant; patients with frontal lesions and right hemisphere lesions reported higher sexual satisfaction and higher function. No correlations were found with cognitive measures or clinical examination. Subjects with more recent injuries and subjects with right hemisphere injuries reported greater levels of arousal.

Hibbard et al. (39) examined sexual response cycle difficulties as well as other aspects of sexual function in both male and female subjects with TBI and without TBI. Men with TBI experienced significantly more difficulties on self-ratings of sexual energy, drive, ability to initiate sexual activity, ability to experience orgasm, and the ability to maintain an erection. Women with TBI experienced significantly more difficulties than women without TBI on self-ratings of sexual energy, drive, ability to initiate sexual activity, arousal, pain during sex, ability to masturbate, ability to experience orgasm, and with vaginal lubrication. This study found significant difficulties in both men and women with TBI in sexual positioning, sensation, and body image variables. Clearly, the findings noted above are dependent on many factors that include cognitive, emotional, interpersonal, physical, and physiological functioning.

The etiologies of sexual dysfunction in TBI are certainly multiple. Sexual dysfunction following TBI may be due to one or more factors, including injury to specific brain regions, neurochemical changes related to this pathology, endocrinologic abnormalities, medications, secondary medical conditions, physical limitations, cognitive deficits, emotional difficulties, behavioral deficits, and interpersonal difficulties.

## DISABILITY AND SEXUALITY

Individuals with disabilities are a diverse group of people, representing a range of sexual expression and orientation, just as is the case in the population of individuals without disabilities. Providers often incorrectly assume that individuals with disability are sexually inactive or neglect to consider the issue of sexuality. In a recent study (53), 94% of the subjects with physical disabilities were found to be sexually active, a rate matching that of non-disabled individuals.

The paucity of information and biases that exist in the medical and scientific literature include myths that individuals with disabilities are asexual, lack sexual desire or attractiveness, are incapable of healthy sexual function, and lack the social and/or problem-solving skills necessary for sexual functioning. In addition, women with disabilities are viewed as less affected sexually than men with disabilities. These myths are not based on scientific data and have been perpetuated by a general lack of knowledge about disability and sexual functioning, although they may still guide healthcare professionals' behavior (54, 55).

The result of this general lack of awareness or bias is that individuals with disabilities may not receive adequate screening, education, or treatment for sexual dysfunction or reproductive health (55). Women with physical disabilities encounter serious barriers to receiving general, as well as reproductive health care, and have difficulty locating physicians who were knowledgeable about the disability to assist them in managing their pregnancy (53).

For individuals with disabilities, the associated features of the disabling condition may adversely influence the assessment and treatment of sexual dysfunction. Incontinence may have a serious impact in their sexual functioning (56). Intellectual or cognitive disabilities may present as an invisible disability. For this reason, healthcare professionals may not recognize the ways in which the disabling condition may affect sexuality and intimacy. Deficits in cognitive and social skills may have a serious effect on self-esteem, and contribute to difficulties establishing and maintaining relationships. An individual with a traumatic brain injury may lack insight, judgment, self-awareness, and perception of others needs or social cues. In other cases, the patient may not initiate conversation with the healthcare provider regarding issues related to sexuality. Individuals with TBI who have attention, memory, and judgment deficits may experience difficulties identifying and describing their symptoms. Conditions can be neglected or misdiagnosed.

For persons with TBI, a combination of cognitive and behavioral deficits may place them at increased risk of exposure to sexually transmitted diseases. Given the risk and potentially serious impact of sexually transmitted

diseases and sexual victimization in persons with disabilities, it is extremely important for healthcare providers to be knowledgeable about sexuality and sexual functioning and to be prepared to open the discussion in the clinical setting. Professionals should perform a careful and comprehensive history and physical that includes information about all aspects of sexuality and sexual functioning as outlined in subsequent sections of this chapter.

Cultural and religious beliefs and values can impact how open the patient will be to discussing sexuality and to accepting information. For example, in many Latino, Asian and Native American cultures, women are not permitted to talk about their sexuality (57). Cultural awareness and sensitivity are essential during any clinical encounter.

### **LESBIAN, GAY, BISEXUAL, AND TRANSGENDER AND INTERSEX INDIVIDUALS**

Lesbian, gay, bisexual, transgender, and intersex (LGBTI) issues in individuals with TBI have received little attention in the literature. Given the diversity among the lesbian, gay, bisexual, transgender and intersex members of society, combined with stigmatization, negative attitudes, and the political climate, population estimates are difficult to obtain. Prevalence estimates range from 5.5% to 20.8% depending on the definition (57).

Sexual prejudice has led to homophobic, heterosexist attitudes and heterosexual-centric attitudes in many areas of our culture including healthcare (57–59). Having a disability and being in a sexual minority places one at risk for discriminatory behavior for multiple reasons. Individuals who are LGBT with TBI may not receive an optimal level of medical care or rehabilitation. For example, lesbian and gay sexuality issues may not be appropriately addressed in sexuality education, examinations, or treatment (59). Intersex or abnormal sexual differentiation conditions and their effects are often poorly understood by medical professionals.

Sexual dysfunction may not be accurately identified due to a lack of knowledge or discomfort among healthcare professionals. Professionals lacking specific knowledge about LGBT issues or holding certain biases may make incorrect conclusions or diagnoses based on inadequate information, especially if the patient feels threatened or lacks trust in the provider. The stress of sexual orientation disclosure and a fear about including partners in the treatment program may result in inadequate or inappropriate recommendations. Concerns regarding confidentiality may limit the amount of information the LGBT individual and partner will disclose, particularly in an interdisciplinary setting, where a team of healthcare providers are providing care.

The incidence of traumatic brain injury in adolescents and early adulthood is significant. During this stage

of development there is a developing awareness of sexuality and TBI “can terminate such exploration” (60). Building a trusting and open relationship with LGBT adolescent patients and using a non-judgmental communication style will both facilitate discussion and identify if the adolescent should receive counseling to facilitate exploration of sexual orientation.

## **NEUROENDOCRINE DYSFUNCTION AFTER BRAIN INJURY**

### **Introduction**

Neuroendocrine disorders occur at a frequency that varies according to research methodologies but is not insignificant. In fact, more recent studies suggest incidence and prevalence rates that are higher than previously reported. Neuroendocrine dysfunction after TBI may include temperature lability, appetite disturbances, hypothalamic and pituitary disorders, disorders of fluid regulation, hypertension, and immunologic disorders. The neuroendocrine system mediates hormonal and neuronal responses to stress, and therefore, a disruption in this system can have widespread effects. Neuroendocrine disorders after TBI are a consequence of specific injury to centers of regulation of physiological functions, represented in many different brain regions, but most frequently the hypothalamic-pituitary axis. Alterations in antidiuretic hormone (ADH), cortisol, growth hormone (GH), thyroxine, follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, glucagon, and somatostatin have been reported (61–63).

The most recognized pituitary hormone abnormality after TBI is a result of effects (which are not well-understood) on the posterior pituitary, resulting in disordered production of vasopressin (also termed antidiuretic hormone or ADH). ADH is released from the posterior pituitary gland in response to hyperosmolarity, hypovolemia, nausea, and other factors and then acts on the renal distal tubule and collecting duct to increase water resorption. Diabetes insipidus (DI) results in excessive urination in conjunction with hypernatremia and hyperosmolarity. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH), associated with hyponatremia, may occur as well. The other major hormonal abnormalities that occur after TBI are the result of anterior pituitary dysfunction.

Until recently, anterior pituitary dysfunction following TBI was considered uncommon, although in the 1980's, Horn reported 28% of TBI patients in a rehabilitation setting had abnormal endocrinologic studies and 12% required treatment (61, 62). More recent studies have shown anterior pituitary damage to be fairly common following TBI. Dysfunction of the anterior pituitary gland may lead to a compromise in growth hormone (GH), thyroid, glucocorticoid, sex hormone (testosterone



in men/estrogen in women), and prolactin production. The clinical presentation of this syndrome varies widely, depending on the particular neuroendocrine axes that are involved, and the severity and rapidity of pituitary damage. Depending on which anterior pituitary hormones are missing, the presentation might range from subclinical disease to marked muscle dysfunction or cardiovascular collapse. Anterior pituitary dysfunction often accompanies posterior pituitary dysfunction (64). Immediate hormonal replacement is recommended for patients with panhypopituitarism, adrenal insufficiency, hypothyroidism, and diabetes insipidus. Replacement therapy includes adrenal and thyroid replacement, anti-diuretic hormone, and if necessary, gonadal and growth hormone replacement. In the case of growth hormone deficiency, retesting is recommended prior to a determination of replacement.

### **Incidence of Hypopituitarism**

What is not clear from research to date are: 1) the implications of deficiencies for each of the axes, 2) the time frames for when these deficiencies develop, 3) the permanency of the deficiencies, 4) appropriate ways of testing for GH.

Two studies (41, 65) indicate that posttraumatic hypopituitarism with permanent hypogonadotropic hypogonadism is a rare complication of TBI. More recent studies question this finding, at least for patients with severe brain injury. The prevalence of post-traumatic hypopituitarism was initially reported over 50 years ago as less than 1%. However, in a more recent study of men with severe head injury, 88% had subnormal testosterone levels at 7–10 days after TBI; 3–6 months later, 24% of a smaller sample still had low testosterone levels with loss of libido and impotence (66). A recent review also suggests the prevalence may be much higher (67). A total of 367 cases (from 1942–1998) were reviewed; the highest prevalence of disorders within the category of hypopituitarism was hypogonadism, hypothyroidism, (over 90% of the sample) and adrenal insufficiency (about 50%). Diabetes insipidus was present in about 30%, and growth hormone deficiency in about 25% of the sample.

Risk factors for hypopituitarism in TBI include moderate to severe head injury (Glasgow Coma Scale of 10 or less), diffuse brain swelling, and a hypotensive/hypoxic episode (although the latter has not been observed in every study). Some degree of hypopituitarism appears to exist in about 40% of patients with moderate to severe head injury, with growth hormone and gonadotropin deficiencies occurring at the highest frequency (68). In a study of 70 adults with traumatic brain injury, 21.7% had evidence of growth hormone deficiency, and 87% had both TSH and free T4 below the mid-normal level. Basal morning cortisol was below normal in 45.7% of subjects.

Hypogonadism and hyperprolactinemia were uncommon in this study population (69).

Recent recommendations at the Global Experts Consensus Panel in Philadelphia included guidelines for assessment of hypopituitarism after traumatic brain injury (70). Patients with moderate and severe TBI should undergo baseline hormonal evaluation at 3 months and 12 months after discharge from the ICU. Adrenal insufficiency and diabetes insipidus should be considered in patients with symptoms. The hormonal screening should include 0900 AM serum cortisol, fT3, fT4, TSH, FSH, LH, testosterone in men and E2 in women, prolactin, and IGF-I. In patients with polyuria or diuresis, urine density, sodium, and plasma osmolality should also be evaluated. Low IGF-I levels strongly predict severe growth hormone deficiency (in the absence of malnutrition). Normal IGF-I levels may be found in patients with growth hormone deficiency; therefore, provocative tests are necessary in patients with another identified pituitary hormone deficit. If IGF-I levels are below the 25th percentile of age related normal limits, provocative testing is recommended.

## **CLINICAL EVALUATION OF NEUROENDOCRINE DISORDERS**

### **Posterior Pituitary Dysfunction**

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is more common than diabetes insipidus (DI). In the case of SIADH, patients are usually symptomatic only when the sodium serum level drops below 125 mEq/L. Symptoms include nausea, fatigue, muscle cramps, and eventually psychosis, seizures, and coma can develop. The workup should include urine and serum osmolalities, and the diagnosis is made on the basis of a finding of inappropriately high urine osmolality in the face of a low serum osmolality. For SIADH, when levels fall below 125 mEq/L, fluid restriction (500–1000 mL/day) is usually sufficient to correct the abnormality, but caution should be taken in elderly patients (71). Furosemide, with replacement of sodium and potassium, is an alternative to demeclocycline, which should not be used in children or in any patient with hepatic disease (72).

DI may occur in mild, moderate and severe TBI. The usual onset post-trauma is 10 days. Facial and basilar skull fractures may be a risk factor, even in the presence of a relatively mild TBI (73). Polyuria and polydipsia are clinical symptoms that may be overlooked in the hospital setting. A high serum sodium level may not be present if the patient has access to water replacement. The best test is a water deprivation test, but an alternative is a spot check of plasma and urine osmolalities, and employ a nomogram to identify the abnormality (73, 74). Hyponatremia may occur as a consequence of cerebral salt-wasting syndrome

or inappropriate secretion of ADH. In the former, water and sodium are not conserved; in the latter, water is conserved. For cerebral salt-wasting, fludrocortisone acetate may be an effective treatment (71).

### **Anterior Pituitary Dysfunction**

Patients with hypothyroidism have cold intolerance, constipation, fatigue, and may have myxedema and bradycardia in later stages; TSH is low. In one study of TBI patients, 21.7% had abnormal T4 and TSH (69).

In the case of hypogonadism, libido is reduced, and impotence, menstrual abnormalities, infertility, breast and testicular atrophy may be present; an AM free testosterone, and estradiol in females and a prolactin level are diagnostic.

Growth hormone (GH) deficiency may present with fatigue, decreased muscle mass, exercise intolerance, and truncal obesity; a GH stimulation test may be diagnostic. Cognitive deficits, including impaired judgment, problem solving, concentration, and memory may be present. In one study of TBI patients, 15% had an abnormal glucagon stimulation test (69).

Patients with adrenal insufficiency from decreased ACTH (Addison's disease) present with weakness, fatigue, weight loss, hypoglycemia, postural hypotension, and occasionally nausea and vomiting and abdominal pain. AM cortisol levels are low, and adrenal insufficiency is based on deficient plasma cortisol response to ACTH stimulation. In TBI, the incidence of low cortisol levels may be as higher than previously recognized (67). An acute phase reaction, with the finding of low cortisol levels two hours after injury has been reported in a series of 400 patients with trauma, including severe brain injury (75). Disturbed sleep may be a manifestation of a more common phenomenon in TBI patients, i.e. dysfunctional cortisol diurnal rhythm (61, 62, 72).

### **Precocious Puberty**

Sexual/reproductive effects of brain injury in children can be identified as either hypogonadotropic hypogonadism or precocious puberty. Klachko and associates (76) reported the case of a 39-year-old man with hypopituitarism due to a severe brain injury at age 4 years. Shaul (77) reported accelerated growth of pubic hair and estrogenization of the vaginal mucosa occurring within 5 months of a brain injury. Two other cases (girls, ages 3 and 5), were described after traumatic brain injury; both exhibited breast development, pubic hair, and changes in vaginal mucosa consistent with estrogenization (78). The neuroendocrinologic mechanism is postulated to be destruction of inhibitory neuronal pathways into the hypothalamus, with premature activation of gonadotropin-releasing hormone from the arcuate nucleus

### **GENDER DIFFERENCES IN OUTCOME: PROGESTERONE AND ESTROGEN**

Studies suggest that female patients with traumatic brain injury may recover better than males. Laboratory studies in animals suggest that either progesterone or estrogen or both may be protective or even facilitate regeneration (79, 80). The effect in humans seems to depend on the presence of functioning ovaries (81).

Progesterone and estrogen have widespread effects on brain metabolism. Progesterone may be protective during the injury cascade, may correlate with reduced levels of edema, and may increase neuronal survival. The mechanisms postulated for these effects may be through interactions with cytokines, excitotoxicity, apoptosis, GABA, or other factors. Estrogen may also have a neuroprotective or neuroregenerative effect. Ovariectomized female rats with estrogen replacement have improved survival following traumatic brain injury. The mechanism may be cerebral blood flow preservation, with microvascular effects involving a combination of endothelial nitric oxide synthase induction and an antioxidant effect (80).

### **SEIZURE DISORDERS AND NEUROENDOCRINE DYSFUNCTION**

Temporal lobe seizures usually arise from limbic structures, such as the amygdala, that exert a modulatory influence on the hypothalamic regulation of the pituitary. Limbic and brainstem structures contain neurons with high concentrations of gonadal hormone receptors. Approximately 20% of patients with post-traumatic epilepsy have temporal lobe seizures (82). Up to 58% of men with temporal lobe seizure disorders are impotent or hyposexual, and up to 40% of women have menstrual irregularities or reproductive dysfunction, including polycystic ovarian syndrome, premature menopause, hypogonadotropic hypogonadism, and anovulatory cycles (26–28). Estrogens lower the seizure threshold, and frequency of seizures often increases in females at the time of menses and during pregnancy. Temporal lobe epilepsy has effects on the hypothalamic-pituitary-gonadal axis through effects on dopamine. Because dopamine is a prolactin-inhibitory hormone within this system, decreases in dopamine result in hyperprolactinemia.

Hypogonadotropic hypogonadism, accompanied by amenorrhea in patients with temporal lobe seizures, is associated with low levels of luteinizing hormone (LH). Because no hypothalamic disorder has been identified, this abnormality may be due to limbic discharges that result in altered secretion of gonadotropin-releasing hormone (26). Premature menopause also occurs. In polycystic ovarian syndrome, which also is associated with temporal lobe seizures, LH and prolactin are elevated,

whereas follicle-stimulating hormone (FSH) is depressed (28). Men with temporal lobe epilepsy and hypogonadism, unlike those with isolated hypogonadism, may have no improvement in libido or potency when parenteral testosterone is given; however, initial treatment of the epilepsy, followed by neuroendocrine treatment (bromocriptine or pergolide for hyperprolactinemia and testosterone for hypogonadism), is sometimes effective (27).

## COMPREHENSIVE EVALUATION

### Medical History

Evaluation of the patient begins with a careful history including past illnesses, surgeries, and sexual activity and function (18). Many diseases and chronic conditions can influence sexual function (83). Whenever possible and with consent, information should be obtained from the current partner. Cultural aspects should be considered and sensitivity to cultural differences is essential. Questions should focus on the following areas: (1) a review of neurologic, cardiovascular, endocrine, and urologic medical and surgical history; (2) preinjury and postinjury sexual functioning; (3) sexual orientation (4) history of victimization, including sexual assault, domestic violence; (5) substance use and abuse history; (6) current medication; (7) safe sex practices; and (8) reproductive history and contraceptive practices.

The history should define the patient's expectations in regard to sexual activity and functioning, and through the course of the evaluation, information gaps and misconceptions will become apparent. Dependency patterns, lack of self-esteem, and perceptions of unattractiveness should be identified. Education can be provided during the course of the history-taking session and written materials should be provided (84–86). The examiner must be comfortable discussing all aspects of sexuality, including alternative forms of sexual expression and alternative lifestyles (60). A nonjudgmental style is essential; staff training that focuses on attitudinal issues as well as education is recommended for physicians (87).

In regard to sexual functioning, the following areas should be further explored: 1) sexual desire; 2) sensory experience, as related to sexual arousal, and including a history of painful experiences during sexual activity; 3) sexual response including patterns of erections (penile or clitoral) and vaginal lubrication, 4) ejaculation (including forceful ejaculation of fluids from the urethra during orgasm in women); and 5) orgasmic sensations and experiences.

### Psychological Evaluation

A comprehensive evaluation of sexual functioning includes a psychological evaluation. Establishing rapport

with the client or with the couple is essential when discussing sexual issues. A widely used approach in the field of sexuality is the PLISSIT model (88). This approach emphasizes the importance of giving the client permission to discuss uncomfortable sexual issues. It also highlights the importance of helping the client feel comfortable discussing sexuality and intimacy, and other related issues. It is important for clinicians to remember that sexuality and relationship issues are often very difficult for clients and their partners to discuss. The more comfortable they feel during the interview, the more specific and useful the assessment will be. Establishing the etiology of the sexual difficulty provides the basis for the development of an appropriate treatment plan. It is often more comfortable for clients if the interview begins with a review of the medical history, demographic information, marital/relationship and family history and then gradually begins to focus on emotional, relationship, intimacy, sexuality, and sexual dysfunction issues (89).

Although there are many different formats for organizing and conceptualizing information, the Multiaxial Problem-Oriented System for Sexual Dysfunctions (90) is a useful guide. This approach assists the clinician in classifying sexual problems across a number of domains: desire, arousal, orgasm, coital pain, and frequency dissatisfaction. Another category labeled "Qualifying Information" includes sexual practices such as fetishism, exhibitionism, as well as other problems that may interfere with sexual functioning such as substance abuse and severe psychopathology. In addition, problems are classified as lifelong vs. not lifelong to more clearly identify individuals who have a history of relatively normal functioning followed by a period of sexual dysfunction. The circumstances under which the problems occur (global or all situations vs. specific situations) are also documented. This model provides the clinician with a framework in which to conceptualize the individual's sexual dysfunction as the basis for a problem-focused treatment plan. The DSM-IV utilizes a similar model; subtypes of conditions are used to more clearly define the onset of sexual dysfunction (life-long vs. acquired), context (generalized vs. situational) and presumed etiology (psychological vs. combined factors) (8).

The sexual assessment and history should focus on identifying the sexual difficulties and how they function within the individual or the couple's relationship. LoPiccolo and Heiman (91) provide an outline for the interview and suggest using open-ended questions and including information about the client and the primary partner (if one exists) in all domains. It should include information about the client/couple's life situation, adolescent and sexual development, attitudes, and values and beliefs toward sex (both past and current). Information about current behavior, including relationship issues, communication, displays of affection, intimacy, and sexual

orientation, should also be obtained. The clinician must determine specific information about the nature of the sexual difficulty including onset, frequency, circumstances, treatment attempted, and both the client and partner's responses to the problem.

The history must include information about previous psychological problems and treatment, as well as history of physical, emotional, and/or sexual abuse. Current psychological symptoms must be examined, including anxiety, depressive or mood, adjustment, psychotic behavior, personality disorders, and use and abuse of substances. In addition, it is important to obtain information about coping strategies, interpersonal communication skills, sexuality-specific anxieties (e.g. performance anxiety) and social support. Although most of this information can be obtained through an interview, some psychological assessment instruments such as the Beck Depression Inventory-2 (92), the Minnesota Multiphasic Personality Inventory-2 (93) the Millon Clinical Multiaxial Inventory-3 (94) may be helpful. When psychological disorders are identified, they must be treated because they are often significant contributing factors to sexual and relationship difficulties.

The cognitive difficulties experienced by survivors of TBI are well documented in the literature. Problems with attention, speed of processing, learning, memory, and problem-solving/reasoning skills are common and can clearly impact the sexual problem(s) and relationship. If the cognitive issues have not recently been assessed, a neuropsychological evaluation may be helpful. The neuropsychological evaluation may clarify the nature of the deficits as well as compensatory strategies to lessen their impact on the person's functioning. The impact of these deficits can then be incorporated into the treatment plan for the sexual dysfunction.

### Questionnaires

A number of questionnaires have been developed to assess sexuality in more detail than the usual history-taking session. The Derogatis Interview of Sexual Functioning (52) collects information by self-report in the five domains of fantasy, arousal, experience, orgasm, and drive and desire. A general sexual satisfaction score is obtained as well as a total score.

The Golombok-Rust Inventory of Sexual Satisfaction (GRISS) (95) is a 28 item self-report scale, provides male and female scores (two versions) in the categories of vaginismus, anorgasmia, impotence, premature ejaculation, non-sensuality, avoidance, dissatisfaction, infrequency, and non-communication, as well as a total score. This scale examines sexual functioning within the context of a relationship.

Kreutzer and Zasler (43) developed an 11-item Psychosexual Assessment Questionnaire. The items are grouped into 3 domains: sexual behavior; affect and

self-esteem; and relationship issues with a focus on changes in functioning following a TBI.

Another scale originally developed for use in spinal cord injury, but modified and used in TBI, is the Sexual Interest and Satisfaction Scale (SIS) (96). This scale examines sexual desire, satisfaction with sex before and after injury, and ability to satisfy a partner.

For the woman with a history of sexual dysfunction, a number of instruments have recently been developed. These include the Female Sexual Function Index (FSFI) (97), the Female Sexual Distress Scale (FSDS) (98), and the Sexual Function Questionnaire (SFQ) (99).

### Physical Examination

A neurological and general physical examination should be completed, with a focused assessment to identify impairments that may influence communication, positioning, movement, oral ability, and sensory awareness. Aphasias, dysarthrias, aprosodias, and deficits in attention and concentration or memory should be noted. Facial scars, oral and facial movement and visual and hearing impairments should be identified. Range of motion, especially in the proximal lower extremities, must be evaluated, along with movement of the limbs and trunk. Sensation is a crucial aspect of the examination. The genitalia, rectum, and the breasts should be examined. The bulbocavernosus muscles can be palpated in the male, and tested for voluntary and reflex contraction. Anal sphincter tone should be assessed. The cremasteric reflex (L1) and the bulbocavernosus and anal reflex (S2-5) should also be evaluated. In women, a Papanicolaou smear and pelvic examination are essential (44).

### Medication Review

A thorough review of all medications is necessary. The most common cause of impotence in the general patient population is medication. Drug-related effects on sexual function are usually reversible after discontinuation of the drug. Frequently implicated are (1) antihypertensive agents, (2) antipsychotic drugs, (3) antidepressants, (4) anxiolytics, (5) sedatives; and (6) hormonal agents (including contraceptives and tamoxifen).

The most frequent adverse reactions with selective serotonic reuptake inhibitors (SSRIs) are decreased desire, anorgasmia, and ejaculatory delay (100). Impotence is less frequently reported with SSRIs than non-selective monoamine reuptake inhibitors. Trazadone has the highest number of reports of priapism of the antidepressants, and has also been implicated in persistent sexual arousal syndrome in women. High-dose sildenafil may be effective in reducing ejaculatory latency (101).

Antihypertensive drugs may affect sexual function (libido and sexual response) through vascular or neurologic

effects. Alpha- and beta-adrenoreceptor blocking agents can cause ejaculatory failure. Antipsychotic agents may cause priapism, ejaculatory failure, and painful retrograde or spontaneous ejaculations (102).

In addition to the above medications, large number of other agents have been implicated: baclofen, cimetidine, clofibrate, cyproterone, digoxin, estrogen, indomethacin, lithium, metoclopramide, naproxen, phenoxybenzamine, prazosin, and progesterone, to name a few (103).

### Laboratory Tests

Screening tests for sexual dysfunction include sedimentation rate, blood cell count, fasting blood sugar, serum lipids, urinalysis, hepatic function, kidney and thyroid function studies, prolactin and testosterone levels (in both men and women).

Hypopituitarism may be manifested by low levels of growth hormone, thyroxine or cortisol or by hypogonadism. In men, low sperm count, low serum levels of testosterone, and low levels of LH and FSH characterize hypogonadism. Because protein-bound testosterone may be increased by thyroid hormone therapy or cirrhosis and decreased by hypothyroidism or obesity, free testosterone levels or sex steroid-binding globulin may give a more accurate picture. In women, low serum levels of estradiol and low serum levels of LH and FSH characterize hypogonadism. Hypogonadism may be caused by primary gonadal failure, as well as secondary failure at a central level. Klinefelter syndrome, for example, which has an incidence of 1 in 500 men, may be an unrelated cause of low testosterone in a patient with brain injury. The gonadotropin-releasing hormone test is useful in distinguishing hypothalamic from pituitary causes of hypogonadism, although it is not infallible. The clomiphene citrate-provocative test is also used to evaluate the gonadal axis. Single determinations of any of the above levels may not be accurate reflections of function (104).

### Neurophysiologic and Vascular Evaluation

Spontaneous nocturnal penile tumescence and rigidity can be measured in the sleep laboratory using strain gauges, visual inspection, and other measures and is the most accurate technique for measuring erectile function. Rigidometers for evaluation at home have also been utilized (105–107). If no major vascular problem is present, intracorporeal injection (papaverine, papaverine/phentolamine, or prostaglandin E1) can be used as a diagnostic tool (108). If intracorporeal injection testing of penile tumescence is suggestive of a vascular etiology of sexual dysfunction, penile blood pressure using a Doppler method can help to further evaluate (109).

Neurophysiological and vascular studies may further elucidate the pathophysiological underpinnings of

the disorder. Somatic sensory, somatic motor, autonomic, and visceral sensory testing are available in some centers to further evaluate sexual dysfunction. These tests include dorsal penile nerve conduction studies, pudendal somatosensory evoked potential tests, pudendal motor latency, bulbocavernosus and anal reflex latency measurements, and electromyography (corpus cavernosum and somatic), cystometry, and anorectal manometry.

For women, magnetic resonance imaging (MRI) technology and vaginal photo-plethysmograph devices are used for objective measurement of sexual response. Vaginal photoplethysmograph devices measure blood flow or engorgement following response to visual sexual stimulation (4, 110, 111).

### PHARMACOTHERAPY

The following review of the literature focuses on medications that may have potential benefit, as there are no well-controlled studies in patients with brain injury. Clearly much more research is needed to understand the types of sexual disorders that occur in women, both disabled and non-disabled, and effective treatments for these disorders.

Women's sexuality has not been adequately addressed in research to date, but progress is being made. Recently the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) classifications of female sexual dysfunction have been expanded to include psychogenic and organic causes of desire, arousal, orgasm, and sexual pain disorders that cause personal distress (8). The United States Food and Drug Administration Guidance paper<sup>10</sup> details the recommendations for the clinical development of pharmacologic interventions for female sexual dysfunction. Major pharmaceutical companies are now developing agents for female sexual disorders and or post-menopausal symptoms. These include dopaminergic agonists and related substances, melanocortin-stimulating hormones, adrenoceptor antagonists, nitric oxide delivery systems, prostaglandins, and androgens (4).

### Phosphodiesterase Inhibitors

For men, major progress has been achieved in the development of medications for erectile dysfunction by the introduction of phosphodiesterase 5 inhibitors, and these agents have been utilized in a variety of populations with success (112–116). Phosphodiesterase enzymes are ubiquitous throughout the body and participate in a variety of functions. PDE5 is the predominant enzyme in the corpus cavernosum, and plays a significant role in penile erection. Sildenafil, tadalafil, and vardenafil are all potent inhibitors of PDE5. This class of medications is the most effective oral agents for the treatment of erectile dysfunction (117). These medications have led to a significant decrease

in the use of other methods of treatment for erectile dysfunction. Side effects include flushing, headache, dyspepsia, and visual disturbances (112). These medications interact with nitrates, and should not be given to patients on nitrates (118). Improved sexual function and sexual satisfaction appears to be well maintained over years following the initiation of treatment (119).

Antidepressant-associated (SSRI) or antipsychotic-associated sexual dysfunction may be effectively treated with sildenafil or other agents of this class (120, 121).

### Prostaglandin E1

These agents are utilized topically for men with erectile dysfunction to maximize genital smooth muscle relaxation (122). Topical alprostadil (prostaglandin E1) has been recommended for men with erectile dysfunction, and appears to be well tolerated, with the most common adverse side effect being urogenital pain (123). Sildenafil combined with alprostadil administered via the intraurethral or intracavernous route was effective in some men with erectile dysfunction who failed other monotherapy. (Steers, 2003) Topical administration of alprostadil has been utilized in the study of women with sexual arousal and orgasmic disorders and ultrasound studies document clitoral cavernosal arterial changes that may be helpful in diagnosis of underlying pathology, but is not recommended as an intervention at this time (124).

### Dopaminergic Agents

Dopaminergic agents may be efficacious in the treatment of erectile dysfunction, and may be an alternative to treatment with phosphodiesterase inhibitors. Because dopaminergic systems may be particularly vulnerable to traumatic brain injury (especially mesocortical and mesolimbic systems), sexual dysfunction may be associated with decreases in dopaminergic activity. L-dopa was investigated following the observation that patients with Parkinson's disease who were treated with the drug reported increased sexual activity (125).

Apomorphine (a D2 greater than D1 dopamine receptor nonselective short-acting agonist) decreases secretion of prolactin, stimulates production of growth hormone, and induces erections. Apomorphine may act on neurons located within the paraventricular nucleus and the medial preoptic area of the hypothalamus (126). A MRI study (placebo-controlled) demonstrated frontal limbic area activity after administration of apomorphine (127). A PET study has demonstrated cerebral activity in the right prefrontal cortex (128). Used in research to establish potential efficacy of longer-acting agents (129,130) the drug is now licensed in some countries, for the treatment of erectile dysfunction, in a sublingual

formulation. Side effects are nausea, dizziness, diaphoresis, syncope, and hypotension. The drug interacts with nitrates, increasing the risk of hypotension. Apomorphine combined with phentolamine was effective in one study and this combination may prove to be an alternative to phosphodiesterase inhibitors (131).

### Hormonal Agents

O'Carroll and associates reviewed the results of investigations of hypoactive sexual desire disorder in women and described it as "the major female psychosexual dysfunction (132)." However, little evidence suggests that the disorder can be traced to hormonal inadequacies in women. Hypogonadal women (with androgen deficiency due to pathophysiologic problems that affect androgen production in the ovaries and/or adrenal glands) do demonstrate an increase in sexual interest after androgen replacement (133).

Androgen substitution should be administered as an adjuvant treatment to counseling in women with low libido only when low androgen levels are due to inadequate ovarian and/or adrenal function in the presence of normal estrogen levels. Administration of androgens to women without low androgen levels who complain of decreased sexual interest or desire is not recommended (134). The "normal" ranges for androgens and estrogens, especially as related to female sexual dysfunction, remain a subject of controversy (135). The possible adverse effects from testosterone therapy in women include breast cancer, fluid retention, masculinization (hirsutism, acne, temporal balding, voice deepening, clitoromegaly), and hepatocellular damage (with high doses).

For women, intramuscular or subcutaneous injections, transdermal patches, or topical agents are available. But, again, the only clinical indications for testosterone replacement in women are symptomatic testosterone deficiency following natural menopause, or due to surgical menopause, chemotherapy or irradiation, premature ovarian failure, or pre-menopausal loss of libido with diminished serum free testosterone. Aging is associated with a decline in testosterone in normal premenopausal women (136).

Increasing age may result in a gradual hypogonadal state in men, referred to as andropause. The age of presentation for erectile dysfunction and andropause, or "partial androgen deficiency in aging men," typically occurs in the fifties and beyond, and these health issues may be harbingers for other related diseases such as cardiovascular disease and depression (137). Treatment with hormone replacement is controversial, and a recent statement from Committee on Assessing the Need for Clinical Trials of Testosterone Replacement Therapy of The Institute of Medicine argues for caution. Testosterone can cause gynecomastia, testicular atrophy, congestive heart

failure, and stroke, and can accelerate the growth of prostate cancer (138).

For men, testosterone delivery systems include depot-testosterone, scrotal patches (scrotal or nonscrotal), or a drying gel. Oral administration is associated with hepatic injury. Intramuscular injections, favored by bodybuilders and competitive athletes, produce a fast rise and fall in levels. Testosterone injections biweekly for 6 weeks increased the frequency of sexual thoughts in a group of eugonadal men with low libido compared with placebo. However, no effect was observed in men with inhibited erectile dysfunction (139). Apparently testosterone increases sexual interest in men with pretreatment levels in the normal range. This study also suggests that men with hyposexual sexual desire disorder may benefit from testosterone injections even if serum levels are within the normal range. Additional research is needed, however, because the study included only 20 men.

Human chorionic gonadotropin was used as a treatment in 45 men with erectile failure and 6 men with lack of sexual desire (140). The treatment period was 1 month with twice weekly injections of 5,000 IU or placebo in a double-blind design. The investigators reported that 47% of treated patients had a "good result" compared with 12% of the placebo group; however, they did not separate the cases of erectile failure from the cases of low sexual interest or fully define "good result."

### Antidepressants

Although many antidepressants (tricyclic antidepressants and monoamine oxidase inhibitors) have been noted to cause a variety of sexual side effects, others have been noted to improve sexual functioning in patients without brain injuries, including both serotonin agents and bupropion, which inhibits reuptake of dopamine. Fluoxetine has been associated with orgasm dysfunction (141). Researchers postulate an excitatory mechanism for adrenergic systems and an inhibitory role for serotonergic systems but in view of reports of both increased and decreased sexual functioning, the neurochemical effects are unclear. Trazodone and fenfluramine have been associated with improvement in libido in a number of case reports (142–144), although both also have been reported to cause sexual dysfunction. Bupropion has also been shown to improve libido in individuals with hypoactive sexual desire disorders. In a study of 60 female and male outpatients with psychosexual dysfunction (sexual aversion, inhibited sexual desire, inhibited sexual excitement, and/or inhibited orgasm), 12 weeks of double blind treatment with bupropion resulted in significantly greater improvements in sexual functioning among treated patients than in the placebo group. Only 3% of placebo-treated patients reported improvement compared with 63% of the medicated group (145).

### Opiate Antagonists

Opioids have also been implicated in sexual function. (159) In a small study involving 7 men, 25–50 mg/day led to full return of erectile function as well as nocturnal penile tumescence in 6 patients (32). In a study of 30 men (age 25–50 years) with idiopathic impotence, naltrexone, an opiate antagonist, increased "sexual performance" (defined as intercourse) in 11 of 15 treated patients (31).

### Natural Compounds

A number of compounds from nature have been identified as treatments for erectile dysfunction. These include yohimbine, Citrulline, pyrano-isoflavones, berberine, forskolin, and Korean red ginseng (146, 147). Yohimbine, an alpha-adrenoceptor blocker, has been investigated in multiple studies of sexual dysfunction (148–153). Identifying the cause of impotence (arterial insufficiency) may also identify potential responders to yohimbine (153). Tobacco may negatively influence its effectiveness (149). Yohimbine administered with L-arginine glutamate (a nitric oxide-precursor) resulted in substantially increased physiologic (vaginal pulse amplitude) responses in a group of women with female sexual arousal disorder (154). Similarly, this combination treatment was effective in improving erectile function in male patients with mild to moderate erectile dysfunction (155).

### Other Treatments for Erectile Dysfunction

Intracavernosal injection (papaverine, phentolamine, prostaglandin E1, vasoactive intestinal peptide), transurethral vasoactive agents (prostaglandin E1), vacuum erection devices, vascular surgery and penile prostheses are other therapeutic strategies for erectile dysfunction (156).

Self-injection of papaverine (a smooth muscle relaxant) or papaverine with phentolamine (an alpha-adrenergic blocker) is a treatment modality for impotence due to neurological or vasculogenic causes. Nearly all patients with neurogenic impotence and 60–70% of patients with vasculogenic impotence respond to intracavernous injections (157). Priapism, fibrosis of erectile tissues, hematomas, vasovagal reflex, and chemical hepatitis have been reported (158). Intracavernous injection of prostaglandin E1 is another approach, although painful erection occurs in up to 20% of patients, perhaps related to concentration and/or neuropathy (159, 160). Papaverine (with or without phentolamine) and prostaglandin E1 acts by increasing arterial inflow through vasodilatation and decreasing venous outflow by occluding draining venules, probably through relaxation of smooth muscle in the corpus cavernosum. Unilateral injection results in bilateral effects through cross-circulation.

Prosthetic surgery is less frequently chosen because other alternatives are available for men with erectile disorders. The two major categories of penile prostheses are the semi-rigid and the inflatable prosthesis. Complications include mechanical failure, infection, pain, and perforation, but the rate of complications is now lower because of technologic advances. Other alternatives include vacuum constriction devices, vascular reconstruction, and arterial and venous surgery. Nerve grafts, nerve growth factors, neuroprotection and nerve regeneration, explored at a basic science level, and may offer promise for the management of erectile dysfunction (161).

### Other Alternatives for Women

Lubrication can be effective to promote sexual arousal in women with inadequate secretion and to treat dyspareunia and vaginismus. Some components of the sexual response continuum, including engorgement, elevation, and elongation of the vagina and clitoral erection, are not influenced by lubricants alone. Oral-genital stimulation and the use of vibrators may be helpful for some women.

Zestra for Women is a botanical feminine massage oil (containing borage seed oil, evening primrose oil, special extracts of angelica, coleus forskolin, antioxidants, and vitamin E) formulated to enhance female sexual pleasure and arousal. The formulation has been shown to improve level of arousal, level of desire, satisfaction with arousal, genital sensation, ability to have orgasms, and sexual pleasure in a group of women with and without sexual arousal disorder in a randomized, placebo-controlled, double blind, crossover design trial (162).

## INTERVENTIONS FOR SEXUAL BEHAVIOR DISORDERS

As pointed out by Simpson (163) the literature on sexually aberrant behavior is fraught because of a lack of consensus in defining and delineating the boundaries of such behavior among researchers and clinicians. Documentation of sexual behavior disorders after traumatic brain injury is recorded in surveys and case reports (42, 164–167). Research documents such types of behaviors in animals.

Sexual offending disorders are defined as sexual acts against another person that cause affront or distress (163). These behaviors include touching (frotteurism, toucherism), exhibitionism, voyeurism, and sexual aggression. In one study of 445 patients with TBI, 6.5% were identified as individuals who had committed some form of sexual offense. Alcohol was a factor in only three. The most common offenses were inappropriate touching, followed by exhibitionism and overt sexual aggression (162).

The individual with brain injury may have reduced social skills and this can be demonstrated in disinhibited interpersonal behaviors. These behaviors may cause responses from care providers based on individual sexual attitudes. Unwanted sexual advances may occur and require redirection. Sexual acting out is a result of disinhibition, which creates a variety of inappropriate behaviors and social interactions with sexual implications (84).

The term disinhibition, associated with orbitofrontal injury, presents the underlying force leading to hypersexual, or inappropriate behaviors. Such behaviors are usually described in the context of interpersonal contact but also may manifest as perseverative self-directed behaviors, such as excessive masturbation. Such behaviors may represent response to injury, loss of self-esteem, or need to act out psychological conflict. Changes in sexual preference may represent release of inhibitions from frontal damage (42). Behavior modification may also be helpful in reducing the frequency of some of these behaviors (168).

Sexual offenders have been treated with hormonal therapy such as medroxyprogesterone and other antiandrogens (e.g., cyproterone) that are progesterone derivatives and these agents have been used successfully in treatment of aggressive hypersexual behavior in patients with brain injury to decrease levels of serum testosterone (168, 169). Such interventions have not been thoroughly studied in brain-injured patients, and violent sexual behaviors are rare in this population. Brain-injured persons are more likely to be victims of sexual abuse by others than perpetrators of violent crimes (170).

## SEX THERAPY

Sex therapy focuses on various strategies to improve sexual functioning in both individuals and couples in which one or both partners may have some type of sexual dysfunction. Although sex therapy is more commonly conducted within the context of relationships, individuals without current partners may benefit from some of the techniques used. As previously mentioned, a thorough assessment of the problem(s) is essential to the development of a problem-oriented treatment plan. In this way, sex therapy focuses on the specific area of dysfunction. In addition, sex therapy often involves collaboration between the sex therapist and physicians (171). Therefore, treatment may include medication or change of medications and behavioral and cognitive psychotherapeutic techniques.

LoPiccolo (172) presented the concept of direct treatment of sexual dysfunction which included some basic therapeutic principles such as viewing sexual dysfunction within the context of the relationship, provision of basic sexual education and information, examination about sexual attitudes, addressing performance anxiety, improving sexual communication, improving the partners' ability to



use sexual techniques, prioritizing sexual activity, and providing specific techniques to change behavior. Therefore, in addition to common couples therapy, techniques such as exploration of feelings and direct communication strategies, cognitive therapy techniques such as reframing and coping skills development are also utilized (173).

Behavioral strategies may include increasing affectionate behaviors, relaxation, behavioral rehearsal and/or more sex specific strategies such as desensitization, non-demand pleasuring, directed masturbation, Kegel exercises, non-demand stimulation, start-stop techniques, the squeeze technique, and the quiet vagina exercise (18, 174). Such techniques vary in effectiveness and require intervention by therapists with specific training in both sex therapy and experience in treating individuals with TBI. In this way, standard approaches to sex therapy can be appropriately modified to accommodate any physical, emotional, behavioral, or cognitive impairments that may be present. These techniques of sex therapy may be useful for persons with brain injury and their partners as they explore new ways of relating intimately and sexually to each other.

Treatment of premature ejaculation (PE) is an example of the usefulness of sex therapy techniques. PE is defined as, "Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it . . . the disturbance causes marked distress or interpersonal difficulty(8)." Estimates of incidence vary from 30% to 75% in men and suggest that it is a common problem (175). Given the demographics, cognitive, and behavioral characteristics of males with TBI, PE may be a common but unidentified problem. Treatment of PE can involve several components including an exploration of early sexual or masturbatory experiences in adolescence or young adulthood that may have reinforced rapid arousal and ejaculation as well as interactions within a sexual relationship that may be reinforcing or influencing decreased ejaculatory control. Specific information about the frequency of PE, sexual expectations and their negative effects, and the usefulness of improving communication during sex are also helpful. Treatment may also include masturbation exercises coupled with techniques such as the squeeze technique, visualization or relaxation exercises, the start-stop technique, and graduated steps to increased stimulation. Using these approaches within the broader context of sex therapy can lead to good outcomes for these individuals and their partners (175).

### PROFESSIONAL AND PATIENT EDUCATION

For many individuals and couples, the essential aspects of programs addressing sexuality are education and counseling. In both disabled and non-disabled populations,

lack of education may result in problems establishing and maintaining healthy intimate, sexual relationships. Loss of sexual capacity may be related to failure of the rehabilitation program to address sexuality needs of clients (40). The goal of rehabilitation is to look holistically at the person with a disability and this perspective includes sexuality (176). Quality of life is a goal of rehabilitation and a commitment to including sexuality education as a component of information provided is essential. Education is an integral component of inpatient, outpatient, and residential programs.

Educational program development and implementation requires that healthcare professionals are knowledgeable and comfortable discussing the topic, and value the importance of addressing sexuality. The healthcare professional must have an awareness of the perceptions and feelings that may influence communication of information to patients, partners and families. Barriers identified that result in sexual education not being addressed in healthcare settings include inadequate knowledge, a perceived lack of time, an assumption that someone else is providing the education, and poor patient/family readiness to learn (177).

Staff education can be a method of exploring staff attitudes, awareness, and values. Key goals of education are to increase both the staff's comfort level and knowledge and to gain skills in communicating about sexuality with their peers, patients and families. Discussions can explore the normal development of sexuality throughout the life cycle, human sexual response, cultural differences, and the impact of traumatic brain injury on sexual function (178, 179). In a recent study, results indicated that persons with traumatic brain injury had more negative feelings about their sexuality and relationships than did participants without brain injury. Education in sexuality and ego adaptability for persons working with them is identified as a need (180).

Determining the best time for presenting information and education related to sexuality for the person with brain injury and partners and families is subject to debate, but is probably best provided in the early phase after injury. Sexual dysfunction can develop later in recovery, and follow up with patients regarding sexual function, and integration of prevention programs is essential program components (181). Lack of awareness of deficit can be prolonged, and education is helpful before and after return to the community (182). Nevertheless, learning readiness needs to be determined on an individual basis. The timing, topic areas, amount and method of education should be individualized.

In some settings, sexuality is not addressed until socially inappropriate behavior occurs. Common behaviors seen in persons emerging from coma may be touching genitalia, and self-stimulation, including masturbation. As the individual regains speech, verbal expression that

includes sexual references may occur. Patients may be disinhibited and express sexual feelings to staff or family members. Privacy, safety for patients, and education and support are critical. It is important for partners and families to be prepared for such behaviors. Staff are the most common targets for inappropriate social behaviors. Education is important for all members of the treatment team in inpatient and outpatient settings (163, 183, 184).

Health promotion and prevention is essential. Key topics to include in education of patients and family are potential changes after TBI that may impact sexuality. Of crucial importance is the provision of information about sexually transmitted diseases, including gonorrhea, chlamydial infections, herpes simplex viral infections, syphilis, parasitic infections, hepatitis, genital warts, urethritis, prostatitis, and acquired immunodeficiency syndrome. Safer sex practices include a careful selection of partners, mutual screening as necessary, and use of condoms and spermicides. Information on contraception should be provided, as well as strategies to address memory and compliance challenges due to cognitive impairments (84). Individuals with brain injury are at increased vulnerability to sexual abuse (170).

Education to prepare the person with brain injury for optimal independent living, making informed choices, and socially appropriate behavior will facilitate a successful sexual adjustment (178). Addressing issues of self-esteem directly may be helpful (184). Social and communication skills, integral to initiating and sustaining relationships, should be included in education. Clinical practice guidelines for interventions may be helpful. Three psychosocial components of the guidelines are one-to-one verbal interpersonal skills, one-to-one nonverbal interpersonal skills and strategies to deal with rejection. The guidelines provide specific interventions to foster the development of necessary social skills in long-term traumatic brain injury clients (185).

Education on psychosocial and sexual issues can be accomplished through group education meetings, social skills groups, family/patient meetings, community skills training, and individual or group counseling (182). Role-playing and more concrete and structured, repetitive styles are better choices for presenting education (38). The group setting for patient education also provides experience with improving social skills. Treatment is adapted to the level of awareness of the individual (182). Identifying the person's preferred learning style is important, as well as combining various teaching methods to improve retention of the information. Providing written materials, at an appropriate reading level and font size, are particularly important when there are cognitive impairments.

An interdisciplinary team approach, with all professional staff prepared to discuss sexuality issues in an atmosphere of permission is ideal. Leadership that fosters a team approach with the expectation that sexuality edu-

cation is consistently delivered as part of the program will result in the best outcomes (178).

The PLISSIT model is a structure to guide interventions for sexual counseling and education. Permission (P) can be achieved by simply asking patients an open-ended question to identify concerns. This can be accomplished during the initial assessment and validates for the patient that you are open to discussing sexuality and lead to further questions and dialogue. Limited Information (LI) may include factual information related to concerns such as how the disability can affect sexual functioning. Specific Suggestion (SS) may include information on problem solving or when to seek medical attention/intervention. Intensive Therapy (IT) is individualized treatment provided by sex therapists and counselors. This model recognizes that there may be individual comfort levels and abilities among staff members (88, 176, 177).

A sexuality education program should include both professional and patient/family educational components and be integrated into the interdisciplinary rehabilitation programs in both inpatient and outpatient settings. A comprehensive sexuality education program, implemented in the Statewide Head Injury Program in Massachusetts, outlines both staff and patient education programs, implemented in residential and day treatment programs for adults with traumatic brain injury. Components of the program include patient and staff needs assessments and evaluation measures, and policies and procedures. Sexuality education for staff occurs at the orientation level with advanced level workshops and professional readings programs. Patient education classes are presented in a style adapted to enhance learning, with various strategies in written, question and answer format with prompt feedback and reinforcement, role-playing, and pre-post testing (186).

## REPRODUCTIVE ISSUES FOR WOMEN WITH BRAIN INJURY

A full discussion of reproductive issues for women with brain injury is beyond the scope of this chapter. However, a number of articles and books, written by women with disabilities, are useful for persons with brain injury as well as the professionals who care for and advise them. Although the specific effects of the brain injury on pregnancy, labor, and delivery have not been investigated, other sources offer practical recommendations (86, 187, 188).

Several issues with particular relevance to women with traumatic brain injury are addressed below, including (1) amenorrhea, (2) seizure disorders and anticonvulsant medications, (3) other drugs with teratogenic potential, (4) management of pregnant women in coma or vegetative state, (5) contraception, and (6) infertility.

### **Amenorrhea**

Although female reproductive dysfunction after brain injury is largely unstudied, amenorrhea is frequently observed. Hypopituitarism after head trauma results in amenorrhea, among other clinical signs, but many cases of amenorrhea after brain injury are not associated with hypopituitarism. A pregnancy test should be performed initially when indicated. A low or normal serum prolactin level indicates anovulation, and medroxyprogesterone for 5–10 days will produce withdrawal bleeding, indicating stress and trauma as a likely cause. If there is no response, then a serum LH and FSH level should be obtained. A low or normal level may indicate hypopituitarism or hypothalamic disorder. Consultation with an endocrinologist or gynecologist is recommended.

### **Seizures and Pregnancy**

The risk of malformations associated with use of anticonvulsant drugs during pregnancy in women with epilepsy is clear (189). The absolute risk of major malformations in neonates exposed to anti-epileptic drugs in utero is 7–10%, which is 3–5% higher than for the general population. Barbiturates and phenytoin are associated with congenital heart malformations and craniofacial anomalies. The fetal hydantoin syndrome is further characterized by prenatal and postnatal growth deficiencies, mental retardation, and limb defects; less often microcephaly, ocular defects, hypospadias, and hernias may be caused by other epileptic agents (190). Valproate and carbamazepine are associated with spinal bifida and hypospadias (191). High daily dosage, high serum concentration, low folate levels, and poly-therapy are additional risk factors (189). Infants of epileptic mothers may develop hemorrhagic disorders, apparently due to a deficiency of vitamin K-dependent factors (192). Despite such risks, 90% of women with seizure disorders deliver normal infants.

Because teratogenicity of anticonvulsant medications is associated with elevated levels of oxidative metabolites, an enzymatic marker may be useful in determination of risk. Low enzymatic activity was found in 4 of 19 fetuses, and the predicted high risk for fetal hydantoin syndrome was confirmed postnatally (190).

The risk of seizures during pregnancy, labor, and delivery is increased in 40% of women with epilepsy, although 50% have no change and 10% have a decrease in seizures (193).

In one study, however, 68% of pregnancies in which seizure frequency increased were associated with non-compliance with treatment recommendations (194). Pregnancy can affect anticonvulsant levels, which decline over time, because of emesis, decreased absorption, and due to increases in plasma volume, liver metabolism, and renal clearance. In addition, hormone changes may lead to increased seizures, and protein binding may be altered.

The International League Against Epilepsy (ILAE) published guidelines for the care of women with epilepsy who may become pregnant (195). The recommendations include: counseling about the risk of seizures, bleeding, and toxemia in pregnant women; counseling about malformations, prematurity, seizures, and developmental disorders in fetus and infant; ultrasound evaluation for neural tube defects, heart malformations, and craniofacial anomalies, and amniotic fluid analysis of alpha-fetoprotein for neural tube defects; counseling about options for termination of pregnancy; careful choice of anticonvulsant and monitoring of anticonvulsant levels, both during pregnancy (when they may decrease) and after delivery (when they may increase); adequate amounts of folate (192, 196).

Anticonvulsant drugs have different rates of transmission in breast milk: 5–10% for valproate, 30% for phenytoin, 40% for phenobarbital, 45% for carbamazepine, 60% for primidone, and 90% for ethosuximide (195). Other medications, including antidepressants, antipsychotic agents, and antimigraine medications, prescribed to persons with traumatic brain injury with relative frequency, may have adverse effects on the fetus. These include antidepressants, antipsychotic agents, and antimigraine medications (197).

### **Coma and Vegetative State**

Pregnant women with moderate to severe brain injury who are hospitalized in trauma centers may be in coma, vegetative state, or be classified as in a state of “maternal brain death” during pregnancy. Some may emerge from coma during pregnancy, but a small percentage, evolve into and remain in a vegetative state. Both maternal survival and emergence from the vegetative state are possible. Medical as well as ethical and legal questions are raised.

Dillon and associates (198) recommend maternal life-support measures at 24–27 weeks of gestation, followed by cesarean section at 28 weeks, but no extraordinary measures at less than 4 weeks for mother or fetus. Others (199) recommend continued maternal support until 32–34 weeks to increase survival rates. Obviously, for the fetus that does not survive the trauma suffered by the mother, the pregnancy must be terminated to save the mother's life. Experimental evidence suggests that the fetus may be less vulnerable to acute asphyxia than the mother. Redistribution of blood flow to vital organs, anaerobic metabolism, and decreased oxygen consumption may be the essential mechanisms (200).

### **Contraception**

Options for contraception are not usually limited by medical considerations in patients with brain injury. Poor patient compliance because of memory difficulties may

dictate choice; oral contraception may be ill advised for this reason. Long-acting injectable techniques may be preferable; permanent solutions, if desired, include vasectomy and tubal ligation. Subdermal delivery of the synthetic progestin levonorgestrel has a failure rate of 4 or 5/1,000 users/year compared with 20–50/1,000 users for oral contraceptives; for persons taking phenytoin or carbamazepine, pregnancy rates are higher (201). Oral hormonal contraception may increase the risk of venous thrombosis, and this must be considered in women historically or potentially at risk (84, 86).

### Infertility

In patients with traumatic brain injury, initial evaluations should include hormonal assays, including LH, FSH, prolactin, thyroid function studies, and total testosterone. Low concentrations of LH, FSH, and testosterone suggest hypopituitary or hypothalamic injury, and a releasing hormone stimulation test should be conducted. Hypothalamic ovulatory dysfunction may be treated with clomiphene citrate, menotropins (human menopausal gonadotropins or LH and FSH), or gonadotropin-releasing hormone. In men, hypothalamic-pituitary failure may be treated with menotropins, human chorionic gonadotropin, or gonadotropin-releasing hormone. Testosterone promotes virilization and may enhance sexual function but has no effect on spermatogenesis.

### CONCLUSION

This chapter has focused on the pathophysiology of sexual dysfunction and the contributions of medical, psychological, social and cultural factors that influence sexual functioning in disabled populations. Whenever possible, we have attempted to focus on the specific needs of the TBI population. Updates for the evaluation and treatment of sexual dysfunction, depending on etiology, are provided to practitioners in the field of rehabilitation. Other areas of focus have included neuroendocrine disorders and women's health care in regard to both sexuality and reproduction in this population. Further research is needed to further clarify the incidence and prevalence of these disorders, and effective treatment approaches for optimal outcomes for this population of men and women with disabling injury. In addition, additional attention to the needs of sexual minorities, including gay, lesbian, and transgendered individuals is required to further advance our understanding of sexuality across the entire disabled and non-disabled population. Despite gaps in our basic science and clinical knowledge base, major advances over the last decade have been made in the evaluation and treatment of sexual, reproductive, and neuroendocrine dysfunction that will be of benefit to our

patients with traumatic brain injury. Rapid development in these areas of research will no doubt lead to many new interventions in the not too distant future.

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# 38

## Post-Traumatic Pain Disorders: Medical Assessment and Management

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### INTRODUCTION

The medical management of pain in persons with traumatic brain injury (TBI) is fraught with challenges that are multidimensional in nature. The co-occurrence of pain with TBI has been found to be a common phenomena (1, 2). Clinicians evaluating patients with TBI with comorbid pain complaints need to be aware of the types of neurological, both peripheral and central, as well as orthopedic injuries that may result in post-traumatic pain syndromes in this patient population. Adequate assessment and optimal treatment will typically require a multidisciplinary neuromedical and an interdisciplinary rehabilitation approach.

### NEUROANATOMY AND NEUROBIOLOGY OF PAIN

The neuroanatomic systems involved in pain perception are complex and dynamic (i.e. plastic) and differ in many ways for acute versus chronic pain states (3). The nociceptive system is now recognized as a sensory system in its own right. There are multiple redundancies and feedback loops for both ascending and descending inhibition or facilitation. Important structures include the peripheral afferents, the dorsal horn (replete with its complex interneuronal pool), ascending spinal tracts, descending

spinal tracts, brain stem structures (including the periaqueductal gray, pontine and mesencephalic reticular centers), thalamus, primary sensorimotor cortex, paralimbic and limbic structures (4). Much of the cerebral cortex is involved with processing different aspects of pain.

### Ascending Systems

Pain receptors are located throughout the peripheral somatic and visceral systems. They are sensitive to almost any mechanical, toxic, metabolic and thermal injury. Peripheral afferents are unmyelinated C and myelinated A  $\delta$  neurons with cell bodies in the dorsal root ganglia. These enter the spinal cord at the dorsal horn (DH). Pain receptors and the primary afferent neurons are also affected by peripheral inflammatory processes and mediators released during tissue injury. These mediators may lower the threshold for firing of the primary afferent neurons, perpetuating or augmenting peripheral pain input to the central nervous system. This process is called peripheral sensitization. The nociceptors themselves may release bradykinin, serotonin, substance P and histamine that, in turn, increase the sensitivity of the receptor. In addition, inflammatory mediators such as leukotrienes, cytokines, prostaglandins and potassium from injured cells or via the inflammatory cascade contribute to increased sensitization of the nociceptors and peripheral afferents (5).

Traditionally, the ascending systems of the central nervous system begin in the dorsal horn of the spinal cord (DH). The direct pathway, also referred to as the lateral pathway or neospinothalamic tract, begins in the nucleus proprius (lamina III and IV) of the DH where the second order neuron crosses over in the anterior white commissure to the lateral funiculus of the opposite side, forming or joining the spinothalamic tract. This cross over occurs over 1–3 levels above the afferent spinal level. The second order neuron ascends to the ventropostero-lateral (VPL) nucleus of the thalamus where a third order neuron projects to the primary sensorimotor cortex of the parietal lobe. It is believed that fine discrimination of the type of nociceptive input and location is largely the function of this tract.

However, there are also other, much more polysynaptic ascending pain systems referred to as indirect pathways and which comprise a medial pain system. These principally mediate the autonomic, endocrine, arousal and emotional aspects of pain perception. Unlike the lateral system, these ascend bilaterally, have poor somatotopic organization, and synapse over multiple levels of the neuroaxis. The paleospinothalamic tract leaves the DH and ascends bilaterally in the ventrolateral spinal cord to synapse in the reticular formation, the midline and intralaminar nuclei of the thalamus (including the dorsal medial nucleus) and then project diffusely to limbic structures including the anterior cingulate gyrus. Associated tracts include the spino-reticular tract that ascends in the anterior white matter of the spinal cord to synapse in the medullary and pontine reticular nuclei, which then project to the midline and intralaminar nuclei of the thalamus and then project on to the cortex and limbic structures. The other major paleospinothalamic tract is the spinomesencephalic which projects from the DH to the periaqueductal gray (PAG) of the mesencephalon, then to the midline and intralaminar nuclei, and on to the cortex and limbic system. Both the periaqueductal gray and the reticular nuclei generate important descending modulatory tracts to the DH and its interneuronal pool.

The dorsal horn (DH) is the origin of second order neurons ascending to multiple levels of the central nervous system and which synapse locally with a variety of interneurons as well as the primary peripheral afferent. The synapse between the first and second order nociceptive neurons is subject to both facilitatory and inhibitory inputs from these interneurons, as well as, descending influences from the brain. Ascending neurons largely consist of nociceptive specific neurons and “wide dynamic range” neurons that receive input from both nociceptive and non-nociceptive afferents (6). There is substantial local (peri-segmental) interconnectivity via interneurons, accounting for spinal motor reflexes whereby a noxious input causes withdrawal via anterior horn (motor) neurons.

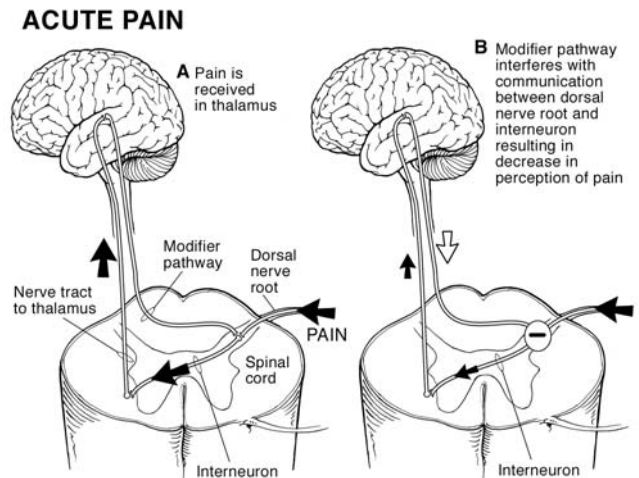


FIGURE 38-1

Proposed pathways for acute pain transmission

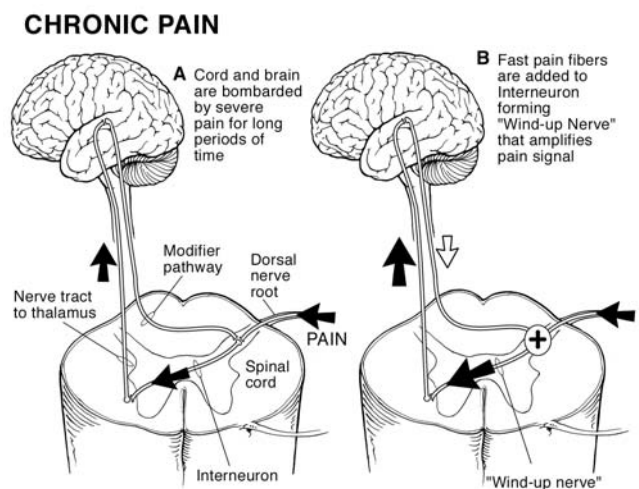


FIGURE 38-2

Proposed pathways for chronic pain transmission

As discussed above, the primary peripheral nociceptive neuron may become sensitized by local tissue injury. It may also begin to develop spontaneous ectopic discharges that may also appear in a region near the dorsal root ganglia (7). Wind-up refers to a progressive increase in magnitude of C-fiber evoked responses in the dorsal horn neurons produced by repetitive firing of the C-fibers and the dorsal root ganglia. This process does not persist after a stimulus ceases, and seems to be related to activation of NMDA receptors and is akin to kindling in some forms of complex partial epilepsy. Wind-up is theorized to occur when successive synaptic depolarizations of the voltage dependent NMDA receptor lead to magnesium depletion; thereby, allowing an influx of intracellular calcium which in turn activates protein kinases and

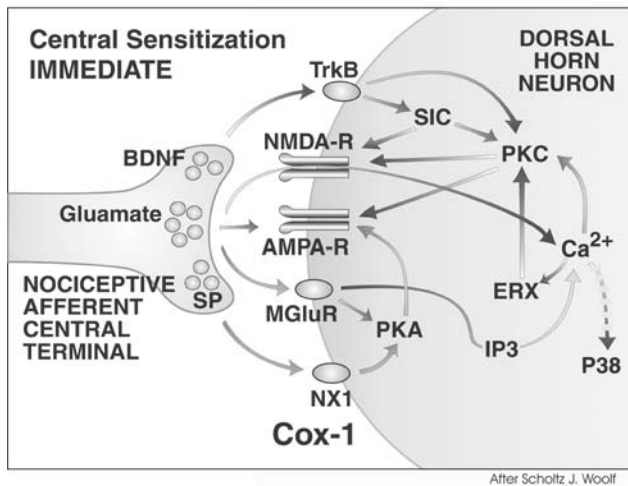


FIGURE 38-3

Theorized mechanisms of central sensitization, immediate

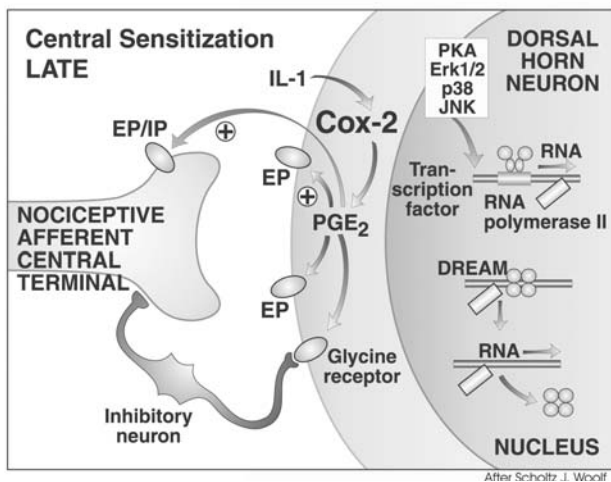


FIGURE 38-4

Theorized mechanisms of central sensitization, late

ultimately causes further amplification of nociceptive responses to stimuli (see Figures 38-1 and 38-2). Ectopic impulse generation after nerve injury is associated with increased expression of messenger RNA for certain voltage-gated sodium channels leading to increased accumulation of sodium channels at sites of ectopic impulse generation, decreasing the neuron’s threshold for firing (7).

Central sensitization is a related phenomenon which, at the spinal level, refers to increased excitability of dorsal horn neurons associated with increased spontaneous activity and decreased firing thresholds in response to primary afferent inputs. The receptive field for the involved dorsal horn neuron also expands. Sensitization of dorsal horn neurons may persist after a stimulus stops, often occurs after tissue injury, and contributes

to secondary hyperalgesia whereby there is increased excitability of nociceptive spinal cord neurons to stimuli outside of the injured area (8). Different mechanisms have been theorized to be responsible for immediate/early central sensitization versus late central sensitization (see Figures 38-3 and 38-4).

Both wind-up and central sensitization contribute to allodynia — the perception of pain from otherwise neutral stimuli — particularly when the wide dynamic range neurons are affected. Furthermore, both peripheral and central sensitization may contribute to sympathetically mediated complex regional pain syndromes. The clinical implications for windup and central sensitization are that they can be minimized by early and thorough pain management (9, 5). As an example, in treating chronic migraine patients, it is imperative that attacks be aborted early. Triptans may not be effective once cranial allodynia has occurred (10).

The neurochemical milieu of the dorsal horn is no less complex than the anatomy. Of the neurotransmitters that we can manipulate with present-day medications, opioids, serotonin, GABA, and norepinephrine all have receptor sites throughout the pain neuro-axis. Although some are primarily pro or anti-nociceptive, some have mixed effects depending on the site of action and the subtype of receptor present. Furthermore, it does not appear that the traditional concept of “one neuron, one neurotransmitter” is valid. Several neurotransmitters may be released from a single neuron, or neuronal system.

At the synapse between the peripheral afferent fiber and the nociceptive or wide dynamic range neuron in the dorsal horn, the pre-synaptic primary afferent may co-release glutamate, substance P, neurokinin A, and calcitonin gene-related peptide (CGRP). These neurotransmitters are all stimulatory to the dorsal horn neuron and are largely considered pro-nociceptive. The presynaptic afferent terminal also has opiate ( $\mu$ ) and  $\alpha 2$  noradrenergic receptors that are inhibitory to the release of the aforementioned neurotransmitters and are considered anti-nociceptive. In addition, the presynaptic terminal has 5-HT<sub>3</sub> serotonin receptors that facilitate the release of Substance P.

The dorsal horn neurons themselves are influenced by neurotransmitters released by cells other than the peripheral afferent fibers (PAF). GABA interneurons (A and B) inhibit the firing of the Dorsal Horn cells. 5-HT<sub>3</sub> also facilitates the GABA interneurons. Stimulation of  $\alpha 2$ ,  $\mu$  opiate, and 5-HT<sub>1a</sub> receptors on the DH cell also inhibit its firing. Some of these chemicals originate from descending inhibitory pathways in the dorsal lateral pontine catecholamine cell groups (DLP) or the rostral ventromedial medulla (RVM). Therefore, within the DH,  $\alpha 2$ ,  $\mu$  opiates, 5-HT<sub>1a</sub> and GABA are all anti-nociceptive; 5-HT<sub>3</sub> has mixed effects, facilitating release of pro-nociceptive transmitter release from the peripheral afferent neuron, but also facilitating release of GABA. Glutamate, substance P,

neurokinin A, and CGRP are all pro-nociceptive (Rao, 2002). Therefore, from the perspective of clinical pharmacologic interventions, those agents that result in net stimulation of opiate,  $\alpha_2$ , GABA, or 5HT<sub>1A</sub> receptors, or that block Substance P, Glutamate or neurokinin receptors should all have analgesic properties.

The second order neurons that ascend via the lateral spinothalamic primarily carry pain and temperature sensation from the contralateral body. Visceral pain is largely transmitted via the medial pain system discussed below. A lesion of the spinal cord involving the spinothalamic tract, therefore, will produce a loss of pain and temperature over the surface of the body contralateral to the lesion, beginning 1 or 2 segments below the injury level. Incomplete lesions of the neospinothalamic tract may produce spinal generated central pain syndromes. Similarly, lesions of the thalamus may produce "thalamic pain" over the contralateral body and face, due to abnormal firing in the VPL nucleus.

The paleospinothalamic system carries nociceptive information from the body viscera and is bilaterally represented in the spinal cord and above. Second order neurons synapse rostrally in the periaqueductal gray of the mesencephalon and the parabrachial nucleus of the pons; these pathways then project to thalamic and limbic structures and appear to be involved in the motivational and affective elements of pain, and associated dysphoria. They also have extensive interconnectivity with hypothalamic, limbic, and brain stem structures related to autonomic control. They are closely linked, regionally and functionally, to the nucleus solitarius and afferent nuclei of the trigeminal nerve, which is implicated in vascular headache (see below) (11, 12).

Projections from the periaqueductal gray and parabrachial region ascend rostrally to thalamic nuclei and then to cortex, anterior cingulate gyrus, insular cortex, and/or directly to the amygdala. The PAG appears to be the center of the most powerful antinociceptive neuromodulator system in the brain (13). There is also extensive interconnectivity between the PAG and orbito-frontal cortex; this system may be key to behavioral responses to threat and stress, switching attention away from pain when essential to survival. NMDA receptors in the anterior cingulate and insular cortices enhance persistent chronic behavioral responses to tissue injury and inflammation, without affecting acute nociception in the spinal cord (11). The anterior cingulate gyrus appears to occupy a key position in the affective responses to pain. Interestingly, there is some evidence to support overlap of emotional pain (social rejection) with somatic pain in this region on fMRI (14). The non-dominant ventral prefrontal cortex appears to dampen emotional distress caused by pain through its limbic and anterior cingulate connections. PET and fMRI studies have demonstrated that regional cerebral blood flow (rCBF) increases to

noxious stimuli are almost constantly seen in the secondary somatic (SII) and insular regions and in the anterior cingulate cortex, with slightly less consistency in the contralateral thalamus and primary somatic area (SI). Activation of the lateral thalamus, SI and SII and insula are thought to be related to the sensory-discriminative aspects of pain processing. Bilateral thalamic responses may be related to the generalized arousal from pain. The anterior cingulate does not appear to be involved in coding intensity or location, but rather in the affective, attentional, and response selection behavioral aspects of pain. Allodynia is associated with amplification of thalamic, insular and SII responses with a paradoxical decrease in rCBF in the cingulate. The anterior cingulate may both respond to pain and participate in endogenous pain control circuitry (15). Interestingly, PET studies of 6 healthy volunteers given intravenous fentanyl showed increased rCBF in the cingulate and orbitofrontal and medial prefrontal cortices; these are areas responsive to nociceptive stimuli and are involved in avoidance learning, reward, addiction, visceromotor control, maintenance of attention and pain-related affective behavior. Fentanyl effects appear to be highly localized and specifically affect these areas (16).

Given the susceptibility of these structures to damage in traumatic brain injury, it would seem likely that higher order pain perception and its emotional resonance would be disturbed. Lesions of the primary and secondary tactile sensory cortex, which receives input from traditional lateral spinothalamic projections as well as the medial system, may produce a cortical loss of tactile sensation not confined to pain and temperature, or disturbances in tactile/pain localization.

As indicated above, there are reciprocal connections between cortical, thalamic and limbic structures and the brain stem regions intimately involved in pain transmission. The periaqueductal gray appears to occupy a pivotal function in this regard, influencing other brain stem structures that in turn modulate dorsal horn nociceptive transmission. Stimulation of the PAG leads to inhibition of dorsal horn neurons, an effect mediated by PAG connections to structures in the rostral ventromedial medulla (nucleus magnus raphe, reticular formation) that provide the primary source of spinal 5HT (and inhibitory influences on nociception). The rostral ventromedial medulla (RVM) has a somewhat complex internal relationship between "on" cells and "off" cells. However, the net descending effect is anti-nociceptive via 5HT. Glutamate from the PAG facilitates this outflow, as do intrinsic opioids receptors. Finally, the RVM serotonergic outflow is also facilitated by norepinephrine from the dorsolateral pontine (DLP) catecholamine cell groups.

The DLP is also facilitated by the PAG. Its primary outflow is alpha-2 adrenergic and is anti-nociceptive not only at the RVM, but also through direct NE influences

on the dorsal horn through its descending pathways. The major descending noradrenergic axons originate in the locus ceruleus, subceruleus, and the Kölliker-Fuse nucleus. These nuclei are also the source of much of the adrenergic innervation to the cortex, cerebellum, and limbic system. Whereas approximately 50% of patients with intractable pain can be helped with chronic electrical stimulation of the PAG and thalamic relay nuclei, additional patients may be helped by stimulation of the Kölliker-Fuse nucleus (17).

In addition to classical neurotransmitters, prostaglandins also increase sensitivity of peripheral nociceptors and are also present in the dorsal horn and central nervous system. Cyclooxygenases are enzymes that become active/are produced during any inflammatory process. They convert arachidonic acid to prostaglandins. Peripheral inflammation increases COX-2 activity in the CNS. In the dorsal horn, prostaglandins produced by COX-2 cause increased release of pro-nociceptive neurotransmitters by primary nociceptive afferents and directly depolarize dorsal horn neurons. They also inhibit glycine release, which is typically anti-nociceptive.

A special consideration in traumatic brain injury is the anatomical and functional associations related to post-traumatic head pain (cephalalgia) and neck pain (cervicalgia). Primary nociceptive afferents for the front of the scalp and face comprise the trigeminal sensory system. Afferents from the meninges travel with the “ophthalmic” division of the Vth cranial nerve. The brain itself does not appear to have any nociceptive afferent fibers. The area around the ear and the external auditory canal gives rise to sensory afferents to the IX and X cranial nerves. Finally, the posterior scalp and upper neck are innervated by the upper 3 cervical dorsal roots; the greater occipital nerve C<sub>2</sub> and the lesser occipital nerve C<sub>3</sub>. Nociceptive afferents from the Trigeminal nerve, IX and X travel to second order neurons in the spinal tract and nucleus of the trigeminal nerve, which extends from the medulla to at least C<sub>2</sub>, at times to C<sub>4</sub>. Interestingly, the V1, or ophthalmic division, is most caudal. The upper cervical dorsal horn and the spinal tract of the trigeminal nerve are contiguous and overlap (18). It appears that there is also overlap between the second order neurons in this region as well, so that central sensitization and expansion of receptive fields by second order neurons may lead to perception of pain in the occiput or neck when the primary nociceptive generator is trigeminal, and vice versa. Therefore, a primary nociceptive generator in the cervical musculature of occipital nerves could also activate the trigeminovascular system through central sensitization (19, 20). Central afferent convergence and sensitization of afferent second order neurons may underlie the spread of pain and referral from supratentorial dura to areas innervated by cervical afferents (muscles and joints of the head and neck). This would be the basis for

one theory of referred pain: the “convergence-projection theory” whereby pain originating from an affected tissue (primary nociceptive generator) is perceived as originating from a distant receptive field (21).

In migraine, sensitization of trigeminal meningeal neurons leads to central sensitization and often results in hemicranial allodynia (10). Also, stimulation of the occipital nerve clearly activates spinal nucleus caudalis of V in the same distribution as when the meninges or V innervated structures are stimulated (in the cat)(19). Migraine appears to cause unique activation of the brain stem PAG, as well as, the dorsal raphe nuclei, which provide diffuse serotonin projections to cortex and blood vessels (22).

As with somatic nociceptive inputs, the PAG seems central to pain mediated by the trigeminal system (as in migraine) (23). PET studies demonstrate activation of the PAG, dorsal raphe nucleus and locus ceruleus on the contralateral side headache (24). Capsaicin trigeminal stimulation in rats results in neuronal activation of the trigeminal nucleus, area postrema, solitary tract, reticular nucleus, locus ceruleus, parabrachial nucleus, raphe nucleus, PAG, intralaminar thalamic nucleus and various hypothalamic nuclei as well as the amygdala (25).

The nociceptive systems in the peripheral and central nervous systems are both complex and dynamic and the interplay of PNS and CNS in pain mechanisms is complex (see Figure 38-5). Modulatory effects on pain transmission occur in the spinal cord, brain stem, and thalamus, and occur via interconnections with limbic and frontal structures, especially those with relevance to the affective or attentional aspects of nociceptive processing. Many of the aforementioned sites are also uniquely susceptible to the pathology of traumatic brain injury. The neurochemistry, and hence neuropharmacology, of pain

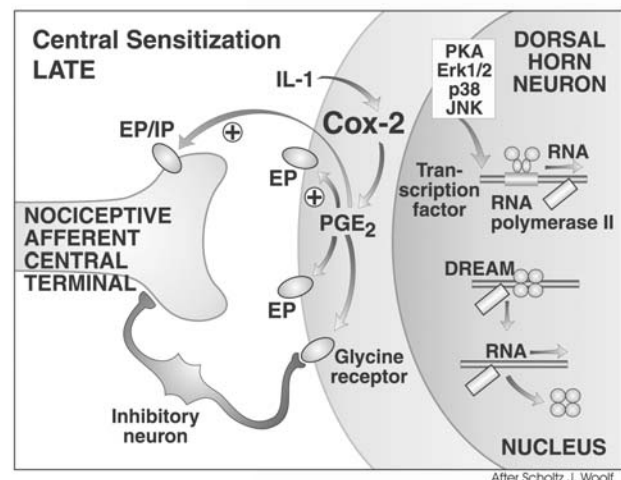


FIGURE 38-5

Interactions between PNS and CNS sensitization pain processes

transmission and perception in the CNS often overlaps that of other disorders related to TBI such as depression, spasticity, and cognitive deficits, making any effort to treat these problems in isolation, without duly diligent awareness of the impact on the neurochemistry of associated conditions, ill advised. The plasticity of nociceptive transmission accounts for central sensitization and may also explain the neurological basis for referred pain. While on the one hand, the pain practitioner may wish to eliminate or control central sensitization, it is possible that the chemical and cytological architecture underlying central pain may also provide the structure for other important "plastic" processes in the CNS, such as motor recovery, learning, and memory. It is not clear whether effective treatment of central pain (when available) will benefit or impede these other neuro-plastic processes.

The neuroanatomical pathways associated with pain perception are clearly complex and not completely understood. Readers are referred to more in-depth sources for further detail (26–28). Cortical pain centers include the somatosensory cortex which receives input from the thalamus which receives its input from the mid-brain nociceptive centers which in turn receives input from brain stem nociceptive neuraxes. Input to the brain stem occurs through the spinothalamic tract which derives its input through both wide dynamic range neurons and nociceptive specific neurons which both compromise second order afferents (4).

The lateral and medial pain systems should also be further considered given the importance of these tracts in mediation of pain processing (27). Vogt and colleagues considerably extended the concept of the medial pain system by demonstrating projections of the medial thalamic nuclei to area 24 of the anterior cingulate cortex. The anterior cingulate cortex is an extensive area of the limbic cortex overlying the corpus callosum and is involved in the integration of cognition, affect, and response selection. The descending connections of the anterior cingulate cortex to the medial thalamic nuclei and to the periaqueductal gray in the brain stem suggest that this system may also be involved in the modulation of reflex responses to noxious stimuli. Partly because of the differences in latency of responses and their respective connections, researchers have suggested that the lateral and medial pain systems are predominantly responsible for processing acute and chronic pain, respectively (29). However, it is evident that these systems are highly interconnected and parallel. Only at the level of the cortex do they become less obviously interdependent. The intensity of sensation and pain perception is directly related to the energy level at the pain location. Primary efferents are composed of A-delta fibers and C-fibers. A-delta fibers are small, thin, myelinated neurons, 1–5 micrometers in diameter with conduction velocities in the range of 5–30 meters per second. Pain mediated by A-delta

fibers tends to be fast, sharp, localized and well defined. These fibers have small receptive fields and tend to be modality specific. They are divided into thermoresponsive and mechanoresponsive sub-groups.

C-fibers are small unmyelinated afferent fibers with diameters of 0.25 to 1.5 micrometers and conduction velocities from 0.5 to 2.0 meters per second. Pain mediated by C-fibers tends to be slow, diffuse, poorly localized and of a burning, throbbing or gnawing nature. These polymodal fibers subserve noxious nociceptive input from thermal, mechanical, and chemical stimuli, as well as, non-noxious, low intensity stimulation. Input to the primary afferents is provided through nociceptors which ultimately are the first step in the sensory pathway of transduction of a painful stimuli to a relevant neural signal. Nociceptors occur in cutaneous, muscular and visceral structures.

Pain may be triggered by sensory inputs, especially when acute, but may also be generated independently, especially when chronic. Sensitization effects represent hyper-responsiveness in either the peripheral or central components of the nervous system. Supraspinal sensitization effects associated with the medial pain system (27) and related limbic structures (30, 31) seem to mediate the pain response. Thus, pain could be produced by the output of a widely distributed neural network in the brain, rather than directly by nociceptive stimuli. Importantly, the central pain control processes seem to encompass the cognitive-evaluative, motivational-affective, and sensory-discriminative systems (32) that characterize the pain response. Finally, it should be noted that "the pain system" is intimately related to other systems in the brain (e.g., motor, mnemonic, social).

## PAIN ASSESSMENT

Pain is a subjective experience and therefore a patient's self-report of pain is in actuality the cornerstone of pain assessment. There are several important aspects of the experience of pain that should be assessed. Pain character, onset, location, duration, and factors that exacerbate or relieve the pain should be explored. The clinician should also query about pain frequency and intensity and interference with everyday activities. Two useful methods of assessing pain intensity in adults are the Visual Analogue Scale (VAS) (33) and the Verbal Analogue Scale. The Visual scale is a 10 cm line with anchors of "no pain" and "the most pain imaginable", while the Verbal Analogue Scale solicits rating of pain on a 0 to 10 scale with the same anchors. The scale appears to be sensitive to treatment changes and is widely used in clinical settings.

Pain is a complex perceptual process comprised of behavioral, affective, cognitive, and sensory components, thereby requiring evaluation of not only the patient's

medical findings, but also physiological, behavioral, and cognitive-affective functioning, including vulnerabilities and strengths. Martelli, Nicholson and Zasler, in chapter 39 of this text, provide a thorough review of the most useful pain assessment instruments, along with a model and method of pain assessment.

Importantly, a comprehensive, multimodal, biopsychosocial assessment becomes critical when pain is chronic, and should address beliefs about the individual's pain condition, pain coping strategies, psychological adjustment, activity level and quality of life (34, 35). The impact of various cognitive processes on the subjective perception of the patient's pain must be considered in the context of a comprehensive pain assessment. Turk has emphasized the importance of understanding and addressing the important role of patient pain appraisals, beliefs and expectancies (36). Furthermore, Dr. Turk has noted that patients who have chronic pain resulting from traumatic events tend to view any physical sensation as harmful and noxious, thereby increasing anxiety, as well as, subjective pain perceptions ultimately leading to further avoidance of activities and greater functional limitations which only serves to facilitate further deconditioning perpetuating this cycle.

Components of emotion that are relevant to the pain experience include: the subjective experience of how the pain feels, autonomic arousal associated with bodily reactions to pain, cognitive appraisal(s) of the painful experience as related to the personal meaning of the pain or the learned responses to pain and injury, non-verbal behaviors including facial expressions and body language associated with pain, and lastly, affective reactions to pain including anxiety (more typical acutely) and depression (more typical chronically) (37). People who have chronic pain have a much higher predilection and incidence of depression, anxiety, as well as, anger. Diathesis-stress models have been proposed to explain the higher rate of depression in this patient population, however, the implications are likely applicable to other psychoemotional responses to chronic pain as well.

Finally, psychological assessment is now a required element of pain treatment programs accredited by the Commission on Accreditation of Rehabilitation Facilities (38) as well as several managed care companies. Again, readers are referred to Chapter 39 in this text for a more thorough review of pain assessment methodology. This chapter includes a survey of general classes and useful pain assessment instruments including a model of assessment based on previous work (39).

## PAIN MANAGEMENT STRATEGIES

The management of pain represents a significant public health issue in the United States. It is both costly to our

health care system and devastating to the patient's quality of life. The need to improve pain outcomes is reflected by the congressional declaration of the present decade as the "Decade of Pain Control and Research," and the acknowledgment in January 2001 of pain as the "fifth vital sign" by the Joint Commission of Healthcare Organizations.

The goal of pain management is to modulate and ideally negate the associated physical and psychological symptoms of pain, prevent chronicity and reduce functional disability. Realistic endpoints of pain relief consistent with the clinical situation should be established. Pain management methods include both non-pharmacologic and/or pharmacologic methods and are optimized when provided in a coordinated interdisciplinary and multidisciplinary fashion (see Chapter 39). Clinicians should strive to identify pain generators and treat them as directly as possible versus simply treating the symptom of pain. The simplest, least invasive, lowest risk and most cost effective management approaches that allow for optimization of patient compliance and maximal functional restoration should be used whenever possible. When pharmacologic agents are used, analgesia should be delivered with minimal adverse effects and inconvenience to the patient, with clearly defined treatment expectancies, all of which will optimize compliance.

### Medical Management: General Considerations

In the acute care setting, already compromised neurological status may limit the array of pharmacotherapeutic agents that might be appropriate to use in a patient where the neurosurgical and neurological status is either stabilized and/or static. Medications that potentially alter any aspect of the neurological assessment should be used with caution in the acute care setting if there is a more significant brain injury and/or neurologic instability. Additionally, consideration should be given to medications with reversible effects (e.g. opiate reversal with naltrexone) whenever there is question of medication effect versus ongoing deterioration of neurological status.

During the acute care phase, the primary pain generators in trauma patients will be fractures, intra-abdominal injuries, soft tissue injuries and pain associated with invasive procedures. Pain treatment should be tailored to the degree of pain assessed and reported via metric (e.g. Visual Analog Scale) or qualitative (e.g. mild, moderate, severe and excruciating) descriptors. For neurologically compromised patients with response limitations, prophylactic pain management should be practiced based upon injuries sustained and clinical presentation. Pharmacologic prophylaxis of pain should be considered in low level patients with TBI (e.g. vegetative and/or minimally conscious) given: a) difficulty in assessment of pain in this patient sub-group, as well as, controversies



regarding pain appreciation and suffering in patient's whose awareness of pain may be difficult if not impossible to confirm and b) the negative impact of pain (even in patients in a vegetative state) related to sub-cortical physiologic responses to nociceptive stimuli including increased tone/posturing, tachycardia, tachypnea, diaphoresis in addition to other adverse effects.

In the sub-acute setting, many of the same issues present in the acute care setting will continue to serve as pain generators. As patients are weaned from pain medication, pain severity can increase and acute pain generators can evolve into sub-acute pain generators. Ongoing attention to pain management must be continued as patients are moved to neurosurgical step-down units and/or inpatient rehabilitation units. Changes in patient status in the sub-acute setting may reflect underlying neural changes that are adaptive or maladaptive. Maladaptive changes can result in additional pain generators (e.g., progression and/or increase of tonal abnormalities resulting in hyper-tonicity and rigidity) as well as central pain phenomena. Pain often affects functional assessment in lower level neurologic patients and must be adequately assessed and treated. This includes pain associated with spasticity, posturing, fractures, pressure sores, peripheral nerve changes, complex regional pain syndrome (CRPS) and post-surgical incisional pain.

Chronic pain has many elements of acute and sub-acute pain but is generally promulgated by additional factors including psychological ones. Current evidence strongly supports mechanisms of central sensitization in chronic pain phenomena which are not present in the acute and sub-acute periods. The patient suffering from chronic pain should be treated just as aggressively as a patient with acute or sub-acute pain, but because peripheral pain triggers are frequently less obvious, with different modalities. With chronic pain, biopsychosocial models for assessment and management are indicated and inclusion and integration of behavioral and psychological interventions usually optimizes treatment outcome.

It is critical in the context of assessment to take an adequate pain history in order for the clinician to provide an adequate foundation for identifying possible or probable pain generators. Clinicians are cautioned against assumptions that commonly reported pain symptoms are due to the brain injury itself (e.g. post-traumatic headache) when pain is more commonly produced by extra-cerebral injury. Evaluating clinicians should be familiar with both the broad array of pain symptoms that may be reported by post trauma patients, as well as assessment methodologies for the various types of pain seen in this population. Clinicians are referred to various other sources for a more detailed description of patient assessment methodologies for persons with pain disorders including dual diagnoses of TBI and pain for more in-depth discussions of this topic (40, 41).

## Pharmacological Management

Mild pain medicines that should be considered typically include aspirin, acetaminophen and non-steroidal anti-inflammatory drugs. For moderate pain the following may be considered: high dose aspirin or acetaminophen, oral NSAIDs, newer generation NSAIDs such as Cox II inhibitors (now limited to the single agent, celecoxib), injectable NSAIDs, mixed narcotic analgesics with aspirin or acetaminophen (with or without caffeine) and tramadol. For severe pain, medications to consider would include: parenteral narcotics (Morphine Sulfate = standard), mixed agonists/antagonists (pentazocine, nalbuphine), partial agonist narcotics (buprenorphine), antidepressants, anticonvulsants, and/or atypical agents. Stimulants such as methylphenidate are used with opioid analgesics as an adjuvant analgesic and to help manage opioid-induced sedation and cognitive impairment. Common medications used in pain management are included in Table 38-1.

Nerve damage with both peripheral and central pain generators is not uncommon in post-trauma patients. Some post-trauma patients may present with both opioid sensitive and opioid insensitive pain at different sites and due to different etiologies. Medications that have been used for opioid insensitive pain include non-steroidal anti-inflammatory drugs (42), tricyclic anti-depressants, newer generation antidepressant agents such as venlafaxine or duloxetine, tizanidine, anti-epileptic medications, and various topical medications (some of which may need to be produced through compounding pharmacies), among other pharmacotherapeutic options.

Adjuvant analgesics are drugs that are analgesic in specific circumstances but have primary indications other than for pain management. Adjuvant analgesics are usually combined with analgesics. Corticosteroids, such as prednisone, are commonly used as short-term therapy to decrease pain and nausea and improve mood, appetite, and general sense of well being. Adverse effects of short-term corticosteroid use include edema, dyspepsia, and neuropsychiatric changes. Diabetic patients should be counseled about careful blood glucose monitoring while taking corticosteroids due to their hyperglycemic effect.

Antidepressants and anticonvulsants are used to manage a variety of neuropathic pain states that have not been responsive to opioid analgesics (see Table 38-4). Tricyclic antidepressants (TCAs), particularly amitriptyline, have shown efficacy in the management of diabetic neuropathy, and are used for other neuropathic states. TCAs can also manage underlying depression in pain states. Other TCAs such as nortriptyline, imipramine, and desipramine are also used. Agents that are SNRIs such as venlafaxine (Effexor) and duloxetine (Cymbalta) have also been found effective in certain pain conditions due to apparent antinociceptive properties. TCA adverse

**TABLE 38-2**  
*Medications for Pain*

ANTIDEPRESSANTS		ANTICONVULSANTS	
<i>Bedtime dose helps sleep and pain</i>		<i>Especially for lancinating/neuropathic pain</i>	
DRUG	TYPICAL DOSE	DRUG	TYPICAL DOSE
Amitriptyline	75 mg qhs	Carbamazepine	200 mg q 8 h
Desipramine	75 mg qhs	Valproic acid	250 mg q 8 h
Nortriptyline	75 mg qhs	Phenytoin	100 mg q 8 h
Fluoxetine	20 mg qd	Clonazepam	0.5 mg q 8 h
Paroxetine	20 to 40 mg qd	Gabapentin	600 mg q 8 h
Venlafaxine	75–300 mg/d	Lamotrigine	100–400 mg/d
Duloxetine	40 to 60 mg/d	Pregabalin	50–100 mg/tid
		Levetiracetam	500–1500 mg/bid
<b>Analgesics</b>		<b>Local Anesthetics</b>	
Acetaminophen	650 mg q 4–6 h	Lidocaine	1.5 mg/kg IV
Tramadol	100 mg q 4–12 h	Mexiletine	225 mg q 8 h
		Flecainide	150 mg q 12 h
<b>Steroids</b>		<b>Topical</b>	
Prednisone	20–80 mg qd	Capsaicin	Topical qid
Dexamethasone	4–16 mg qd	“Speed Gel”	Topical tid – qid

**TABLE 38-3**  
*Opioid Analgesics*

SHORT-ACTING OPIOIDS <sup>1</sup>			LONG-ACTING OPIOIDS <sup>1</sup>		
DRUG	EQUIVALENT DOSES		DRUG	EQUIVALENT DOSES	
	ORAL	PARENTERAL		ORAL	PARENTERAL
Morphine	30 mg q 3–4 h	10 mg q 3–4 h	MS-Contin	90 - 120 mg q 12 h	–
Hydromorphone	7.5 mg q 3–4 h	1.5 mg q 3–4 h	Levorphanol	4 mg q 6–8 h	2 mg q 6–8 h
Codeine	200 mg q 3–4 h	–	Methadone	20 mg q 6–8 h	10 mg q 3–6 h
Hydrocodone	30 mg q 3–4 h	–	Oramorph SR	90 - 120 mg q 12 h	–
Oxycodone	30 mg q 3–4 h	–	Oxymorphone	–	1 mg q 3–4 h
Meperidine	300 mg q 2–3 h	100 mg q 3 h			
Fentanyl	IM or IV		Fentanyl	Transdermal: 25 g patch 45–135 mg Morphine p.o. over 24 h	

Opioid-naïve adults and children ≥50 kg body weight

*Note:* The above mentioned drugs are only a partial listing of available opioids.

effects include anti-cholinergic effects (dry mouth, sedation); weight gain; orthostatic hypotension; and cardiac arrhythmias. Secondary amines such as nortriptyline and desipramine have fewer adverse effects and should be used in patients, such as the elderly, when there is concern for anticholinergic effects, sedation, and orthostatic

hypotension. Antidepressants generally should be initiated at a low dosage and titrated up slowly based on pain relief and patient tolerance.

Anticonvulsants, such as carbamazepine and gabapentin, can be effective for the management of neuropathic pain, particularly lancinating or paroxysmal

pain. Because carbamazepine can decrease platelets, neutrophils, and red blood cells, patients on carbamazepine should have complete blood counts performed routinely. Gabapentin has shown efficacy in diabetic neuropathy and post-herpetic neuralgia, and generally has a milder adverse effect profile consisting of sedation, ataxia, and does not require routine lab work. A recent Cochrane review examining the role of AEDs (anti-epileptic drugs) for acute and chronic pain noted that although they are widely used in chronic pain surprisingly few trials show analgesic effectiveness. They noted that there was no evidence for anticonvulsant effectiveness in acute pain, however, in chronic pain syndromes it was suggested that aside from treatment of trigeminal neuralgia, that AEDs be relegated to basically third line treatment. Lastly, it was noted that there was no evidence to support the contention that gabapentin was superior to other AEDs in neuropathic pain management (43). As with the antidepressants, one should institute treatment at a low dosage and titrate the dose up slowly to improve tolerance and optimize compliance. Valproate, oxcarbazepine, lamotrigine, topamax, levetiracetam, phenytoin and clonazepam are other anticonvulsants that also have been used for neuropathic pain. Newer AEDs, such as pregabalin, an alpha2-delta ligand, recently approved for certain types of neuropathic pain may also prove useful in the management of post-traumatic pain conditions (44, 45).

Newer agents such ziconotide (Prialt), a synthetic neuronal N-type calcium channel blocker, which has received recent FDA approval, may also offer promise for treatment of intractable severe chronic pain in patients intolerant of or refractory to other forms of treatment (46). This agent, like other intraspinal (intrathecal or epidural) analgesics should only be tried when other standard treatments have failed and must be administered via a programmable implanted microinfusion device for long term users. Morphine is the only other agent that is FDA approved for intrathecal use for chronic pain, although other agents including ketamine, midazolam, clonidine and various local anesthetics (i.e. lidocaine and bupivacaine) have been used, alone or in combination, in this application on an off-label basis (47).

Other agents that have more recently been recognized as adjuncts in the pharmacologic management of pain include tizanidine (Zanaflex) and sodium amobarbital (Amytal). Tizanidine has been shown to be effective in a variety of pain conditions including fibromyalgia, as well as, tension type headache, possibly on the basis of modulation of substance P and/or owing to its alpha-adrenergic effects (48). Mailis and Nicholson (49) have provided an excellent review of the use of sodium amytal infusion in the assessment and treatment of chronic pain (and functional disorders).

Capsaicin can be used topically to help decrease pain associated with peripheral neuropathies. Capsaicin

depletes peptides such as substance P that mediate nociceptive transmission. Application of capsaicin is associated usually with a burning sensation, which may be severe enough to require pre-medication with either an oral analgesic or a topical lidocaine cream or ointment. Patients should be counseled not to touch mucous membranes after applying capsaicin.

Compounded agents, typically formulated through "compounding pharmacies" may also play a role in pain management of the patient after TBI. Agents that have been used in topical formulations for pain include: local anesthetics, antidepressants, alpha-2 agonists, opioids, glutamate antagonists such as Gabapentin, calcium channel blockers, skeletal muscle relaxants, capsaicin, Ketamine, menthol, and NSAIDs. Standard topical formulas such as "speed gel", which contains amitriptyline, lidocaine, guaifenesin and ketoprofen, can work quite well for neuropathic/neuralgic scalp pain, scar pain, and post-traumatic myalgias. Similar compounded topicals with varying ingredients such as gabapentin, ketamine and clonidine may be more helpful as adjuvants for CRPS related pain (50).

Surgery produces pain by releasing pain and inflammatory mediators via damaged tissue. This pain is acute pain and will improve as the wound heals and the patient convalesces. The goal of postoperative pain management is to provide continuous and effective analgesia with minimal adverse effects. NSAIDs such as parenteral ketorolac are used both intra-operatively and post-operatively to decrease the production of inflammatory prostaglandins released at the site of injury. The ketorolac dose is dependent on route, patient age, and weight, and should only be continued at the appropriate dosage for five days due to the development of renal dysfunction and GI toxicity. Opioid analgesics are the most commonly used medications for acute and sub-acute post-operative pain, usually administered intramuscularly or intravenously on an as needed basis. This approach can lead to delays in the patient receiving adequate analgesia due to medication administration delays and intramuscular route absorption.

Patients should be switched to oral opioid analgesics when oral administration is tolerated. Patient-controlled analgesia (PCA) is a process where the patient is allowed to self-administer low doses of intravenous opioid analgesics to maintain analgesia. To use PCA, a patient should be sufficiently cognizant to understand the goals of PCA and understand the use of the equipment. Patients who are confused or cognitively impaired are not good candidates for PCA. The number of injections and attempted injections can be monitored for efficacy and adverse effects, in addition to the patient's report of pain. Opioid analgesics can also be administered into the epidural or intrathecal space, combined with local anesthetics such as bupivacaine or ropivacaine for postoperative pain

management. Patient-controlled epidural analgesia may be considered in specific circumstances.

Opioid analgesics stimulate the opioid receptors ( $\mu$ ,  $\kappa$ , and  $\delta$  subtypes) that are widely distributed throughout the brain, spinal cord and peripheral nervous system. The opiate receptors appear to function at pre-synaptic potassium channels and indirectly affect voltage gated sodium channels to reduce the release of excitatory amino acids and substance P. Analgesia occurs primarily via action at the  $\mu$  receptors, and less so at the  $\kappa$  and  $\delta$  receptors.  $\mu$  receptor stimulation is also responsible for some other opiate effects such as miosis, depressed gastric motility, and respiratory depression.  $\kappa$  stimulation does influence spinal analgesia, and also causes miosis and respiratory depression. Stimulation of  $\delta$  receptors seems to account for hallucinations, confusion and stimulation of respiratory and vasomotor centers (51).

Desirable clinical effects of opioid analgesics include analgesia and reduced anxiety. Undesirable effects include sedation, urinary retention, respiratory depression, tolerance and dependence. Circumstantial side effects include euphoria, depressed bowel motility, and depressed cough. Tolerance to side effects develops fairly rapidly as compared to analgesic effects. Tolerance is simply a shift in the dose-response curve to achieve a desired therapeutic effect – one needs to either increase the dose or shorten the dosing interval. This phenomenon is not unique to opiates and occurs with a variety of medications. Physical dependence refers to the phenomena of the body becoming accustomed to the presence of the medication and that an abstinence syndrome may be precipitated by abrupt withdrawal of the medication, again a phenomenon not unique to narcotics (e.g. also seen with SSRI's). In the case of narcotics, abstinence syndrome symptoms may include lacrimation, diaphoresis, nausea and vomiting and typically does not persist for more than 72 hours; however, associated sleep disturbances and depression can last several weeks. Tolerance and physical dependence are simply physiologic responses to opioid exposure and do not imply aberrant drug use. Addiction is a complex set of maladaptive behaviors resulting in physical, psychological or social harm. There is an alteration in central nervous system function which the affected individual finds desirable resulting in a craving for the drug in question, often associated with tolerance for the non-analgesic, desired effect, resulting in unsanctioned dose escalation and preoccupation with acquisition of the drug and resultant adverse psychosocial consequences. The term pseudo-addiction refers to behaviors similar to those in addiction, but more specific to desired analgesic affects. The behaviors cease when appropriate analgesic management leads to adequate pain control (in other words, the physician has failed to provide sufficient medication or alter dosing in response to expected physiologic tolerance) (51, 52).

“Cognitive” and affective side-effects do occur with opiate medications. Euphoria, or dysphoria, sedation, hypnagogic or hypnopompic hallucinations appear typically within 3–7 days of dose initiation or escalation, but abate within the same time frame (52). Any worsening of cognitive performance occurs within the first few days of use, or first few hours after a dose, but tolerance develops to this phenomenon. There are relatively few differences found in cognitive performance in patients taking opioids compared to their performance before opioids or with the performance of a comparable pain population not taking opioids (53). Overall, there is no evidence that there are any long term cognitive side effects from narcotics, and adequate pain control may enhance cognitive performance (54, 51). In a study of 144 patients with low back pain, Jamison administered Digit Symbol and Trail-Making Test B prior to taking opiates and then at 90 and 180 day intervals. Test scores significantly improved while patients were taking opioids for pain (55). Finally, a TBI clinician must consider the fact that the opiate system is intimately involved in learning and reward. In the rodent model, genetic absence of the  $\mu$  receptor, but not the  $\kappa$  receptor, results in severe impairments in spatial learning (56). Therefore, the possibility exists that narcotic use in TBI may not simply be humane (analgesic properties) and without any significant long term negative cognitive consequences, but may also promote certain cognitive or affective improvements. However, practitioners must be aware that there may be adverse cognitive effects in those persons taking undue/excessive amounts of opioid medications, either due to inappropriate physician prescribing practices or patient non-compliance. Other potential reasons for occurrence of opioid related cognitive impairment include drug sensitivity, concurrently use of other substances (e.g. alcohol), or temporary impairment associated with increasing of opioid dose.

There are a variety of derived and synthetic narcotics available, each with different potencies and properties. Meperidine, and to a lesser extent, propoxyphene have mixed opioid agonist and antagonist properties and may cause severe cognitive problems in the elderly, including hallucinations. Neither drug, nor should most narcotics, be used with MAO inhibitors secondary to a risk of hypertensive crisis or autonomic dysregulation. Moderate potency narcotics (hydrocodone and oxycodone) are metabolized by liver P450 enzymes into morphine and if given with other drugs that inhibit metabolism via this enzyme (SSRI's for example) a given dose of these narcotics may produce less than optimal pain relief. Similarly, the low potency synthetic narcotic tramadol should be used with caution with SSRI's and other anti-depressants secondary to increased seizure risk (more likely a function of its agonistic properties on NE and 5HT receptors, that may also be desirable in dampening central sensitization)(57).

The use of narcotics in chronic non-malignant pain management remains controversial. Poppy derivatives and opioid medications have demonstrated proven pain relieving properties for hundreds of years. It has only been in the last century that a significant social stigma has been attached to the use or prescription of narcotics for chronic pain treatment. Now, the pressures from agencies like JCAHO to provide appropriate and thorough pain management appear to be at odds with legislative and legal considerations imposed by State Boards of Medicine. Physicians and patients are concerned about addiction, tolerance, and side effects from narcotics, all of which may generally be more hyperbole than fact although such concerns may sometimes be very real such as in the case where a patient becomes addicted to medication due to inappropriate prescribing or monitoring practices of their treating physician.

Furlan et al. (submitted) (58) have recently completed a systematic review of opioids for CNCP (chronic non-cancer pain) that will serve as the CPSO's (College of Physicians and Surgeons of Ontario) updated guidelines to be released this year (2005). This systematic review of 38 Randomized Controlled Trials (RCTs) concluded that: (1) Opioids are effective in the treatment of CNCP by reducing pain and improving functional outcomes when compared to placebo (2). Opioids are equally effective for both nociceptive and neuropathic pain syndromes when compared to placebo (3). Opioids are effective in fibromyalgia by reducing pain, but did not improve functional outcomes when compared to placebo (4). Opioids were superior to other drugs (e.g., NSAIDs, tricyclic antidepressants), in reducing pain, but failed to improve functional outcomes (5). Constipation and nausea were noticeable side effects more commonly associated with opioids (6). While recent studies indicate development of significant endocrinological abnormalities and erectile dysfunction on chronic opioids, the majority of the studies did not inquire about sexual dysfunction. The only two studies that provided a sexual activity score showed that patients on opioids actually reported they were better in terms of sexual behaviour compared to controls. Improvement of mood or adjustment secondary to better pain control may account for this result (7). However, addiction/abuse in patients with chronic pain can not be assumed not to exist (despite popular statements), because the existing literature a) excluded high risk populations (therefore it is not representative of chronic pain patients seen particularly in pain clinics); b) is methodologically not designed to look for "addiction", and c) the duration of the trials is too short to allow for development of the disorder (even if appropriate definitions and screening tools for addiction had been used).

Most patients taking long acting opioids should be supplied with a fast acting rescue opioid to treat breakthrough pain. Oral rescue medicine may be needed every

2–4 hours. The usual dose is the analgesic equivalent of 5–15% of the 24 hour baseline dose of the scheduled long acting opioid analgesic. As with any pain medication and/or intervention, the prescribed agent should be titrated to achieve optimal pain relief with minimal side-effects. Clinicians should discuss treatment expectancies prior to issuing prescriptions for any pain medication.

Clinicians treating patients with TBI may be especially concerned about cognitive side effects and slowing of cognitive recovery; again, a concern that may be overemphasized. Indeed, for non-brain injured patients with multiple fractures or other injuries, physicians would have no qualms about administering narcotics, especially in the acute care setting. Yet in the acute and sub-acute phases of brain injury, when the patient may be unable to communicate or have severely altered consciousness, physicians are reticent to provide adequate analgesia with narcotics. From a practical perspective, it would be appropriate to use narcotics for analgesia if the physician can reasonably assume that a patient with brain injury has opiate responsive sources of pain, even if they have limited ability to communicate. In fact, a common contributor to "agitation" in the acute care or rehabilitation setting may be inadequate analgesia. On the other hand, there is evidence that patients in a vegetative state do not have conscious awareness of nociceptive stimuli; specifically, there is activation of brainstem, thalamic and primary somatosensory cortices, but not of secondary association cortex (59). The implication is that patients who are truly in a vegetative state (i.e. arousal without awareness) and not MCS may in fact be incapable of "suffering" (in line with historical neurologic community dogma that persons in VS do not feel pain). Opioid analgesic treatment could, however, be considered even in patients in VS if they were experiencing dysautonomic type symptoms from a suspected nociceptive stimulus and/or were manifesting significant physiologic reactivity associated with noxious stimuli including tachycardia, tachypnea, diaphoresis and rigidity. Good clinical care would dictate that every attempt to modulate and/or minimize nociceptive stimuli should be made before using opiate analgesics.

Clinicians should be familiar with important documents concerning the use of controlled substances such as opiate medications. In 2004, the Federation of State Medical Boards of the United States published a *Model Policy for the Use of Controlled Substances for the Treatment of Pain* which was developed in collaboration with pain experts around the country to provide guidance to state medical boards in developing state pain policies and regulations. Written in the form of a model policy document, the guidelines provide model language that may be used to by states to clarify their positions regarding the use of controlled substances to treat pain, alleviate physician uncertainty about such practice and encourage better

pain management. In 2004, the Federation's House of Delegates adopted recommendations and revised the pain policy to reflect new medical insights in pain treatment, particularly with regard to the undertreatment of pain (60). As prescribers, professionals should also be aware of the myriad issues that may confront both the clinician and the patient when opiate medications are utilized for chronic pain management (61). One must also remain aware of the current evidence based medicine regarding the utility of chronic opioid therapies in specific types of pain conditions, such as chronic, non-malignant, neuropathic pain (62, 63).

Current consensus among pain specialists dictates that concerns regarding addiction are generally not a contraindication to opioid treatment for otherwise intractable pain although the possible problems associated with inappropriate opioid treatment should be kept in mind. In particular, the need and efficacy of opioids with chronic pain patients having prior drug abuse histories or addiction prone personalities should be carefully assessed and monitored when being considered for or treated with opiates. The effectiveness of opioids with respect to both reduction in pain severity ratings as well as effect on functional capacity should be considered. Clinicians should always use a "controlled substance agreement" when using such agents for pain management to protect not only the patient's safety but also their own given the litigious nature of our society (64). Ultimately, clinicians must have insight into the fact that chronic pain should be managed in a rational manner via integration of pharmacological approaches with behavioral and traditional rehabilitation interventions (65).

### **General Guidelines for Pain Pharmacotherapy**

The physician should aim for drug prescriptions that optimize compliance and minimize potential side-effects. Particularly in cognitively impaired patients, physicians should aim for once to twice a day drug dosing. Patients should be counseled on the goals of treatment and what to expect regarding adverse effects, especially constipation with opioid analgesics or GI side-effects with NSAIDs. As possible, significant others should also be informed of treatment regimen and possible complications.

Depending on the severity of the pain and the patient's pain tolerance, consider a trial of acetaminophen as an initial management strategy. If prescribing a non-selective NSAID for more than 10–14 days then consider co-administration of a mucoprotectant agent such as a proton pump inhibitor and/or misoprostol. For elderly patients, a gastroprotectant should be used regardless of the duration of NSAID therapy. Only proceed to opiate-like and/or opiate medications when the pain level and functional disability associated with the pain are moderate to severe (42).

When using opioid analgesics, fears regarding dependence should be openly discussed as should any sexual function side-effects. Ideally, the clinician should aim for decreasing polypharmacy, however, when appropriate, combination drug regimens should be considered. It is critical to ascertain whether patients are taking their medicine correctly (e.g. taking scheduled medicine on a prn basis) and/or supplanting their prescribed medications with over the counter (OTC) products.

### **Non-pharmacologic Medical Management**

A wide variety of medical rehabilitative interventions focusing on physical modalities (e.g., physiotherapy, exercise, chiropractic, massage, etc.), as well as, other non-pharmacological medical interventions for chronic pain may be helpful in ameliorating pain complaints and suffering following TBI (66, 67). However, more recent evidence suggests that many such treatments may be of questionable value relative to placebo or no treatment. Depending upon the etiology of the pain generator in question, numerous non-pharmacologic medical and psychological approaches may be considered in the management of pain conditions including use of physical agents and modalities, injection therapies, exercise, biofeedback, adaptive equipment and/or psychological interventions. These treatment modalities should all be given adequate consideration in conjunction with possible pharmacologic alternatives if physicians are to develop adequate functionally oriented treatment regimens for addressing chronic pain issues in persons with TBI. Readers are referred to chapter 39 for details regarding the behavioral and psychological management of pain following TBI.

### **Physical Modalities**

Physical agents utilized to modulate pain may include superficial heat and cold. The most common modalities used are hot/cold packs, heat lamps (incandescent or infrared), paraffin baths and cryotherapy. Hydrotherapy interventions for pain management may involve prescription of whirlpool or contrast baths. Various diathermy techniques may also be utilized to facilitate pain control including ultrasound, phonophoresis, as well as, short-wave and microwave diathermy. There are also a number of electrical stimulation techniques utilized in pain management such as transcutaneous electrical stimulation (TENS) and iontophoresis that are commonly employed as adjuvants for pain control. Although historically used for chronic pain modulation, a recent Cochrane (68) review examining the efficacy of TENS in the aforementioned application found inconclusive results with published trials not providing information on the stimulation parameters most likely to provide optimum

pain relief, nor the effectiveness of long term treatment. A more recent study (69) found that evidence was lacking, limited or conflicting for efficacy in mechanical neck disorder management for electrotherapy interventions including PEMF (pulsed electromagnetic field) therapy, galvanic current, iontophoresis, TENS, diadynamic current, and electrical muscle stimulation. Cranial Electrical Stimulation (CES) is a treatment for pain reduction that, unlike TENS, targets central nervous system function. The technique involves attachment of electrodes carrying microcurrent across the scalp and induces an approximate 15Hz cortical rhythm. Many controlled studies support that it is a safe and useful treatment for pain, especially chronic pain and its associated symptomatology of anxiety, depression and insomnia (70).

Physical modalities tend to play a more predominant role in the treatment of pain complaints of musculoskeletal origin and may include traction, manual medicine techniques (e.g. joint manipulation, myofascial release techniques and strain counter-strain), as well as, massage (71). Body-work techniques and bioenergetics, although not well studied aside from acupuncture, are two additional classes of intervention that may also be used as adjuncts in chronic pain management (e.g. Reiki, Alexander, Trager and meridian, acupuncture, polarity, respectively). Injection techniques including intra-articular, peri-articular, peritendinous, ligamentous/fibrous tissue (i.e. prolotherapy) and trigger point can all be used in various types of musculoskeletal pain disorders (72). Axial injections such as epidurals, zygapophyseal joint, and sympathetic blocks may all be relevant considerations for pain treatment in this population, depending on the presumptive pain generators.

Exercise, is an underappreciated and therefore under-prescribed treatment intervention in persons post-TBI or for that matter many other patients with pain complaints. Exercise can play a significant role in controlling pain both on a central and peripheral basis improving deconditioning that may be resulting in nociception and concurrently improving weight control, affect, and general state of health and well-being (73, 74). Exercise has also been shown to elevate beta endorphin levels as much as five times that of resting levels (75). Additionally, recent information strongly supports the argument that exercise results in up-regulation of brain-derived neurotrophic factor (BDNF) and therefore may play a role in promoting neural repair and enhance learning and memory by increasing neurotrophic support (76). Of course, the benefits of exercise are dependent upon the patient taking an active involvement in rehabilitation.

Adaptive equipment such as reachers, sock aides, long handled scrubbers and/or brushes, as well as, ergonomically modified task analyses for ADLs, mobility and work environments are a few of the many different interventions that may also facilitate greater pain modulation and

tolerance. Appropriate education regarding pacing and energy conservation techniques may also add to further improvement in functional status depending upon the type of chronic pain condition being treated.

## **SPECIAL TOPICS IN PAIN MANAGEMENT IN PERSONS WITH TBI**

### **Post-Traumatic Headache**

#### *Background Information*

Headache (e.g. cephalalgia) is the most common physical complaint reported after mild brain injury/concussion and cranial (i.e. head) trauma. Headache is also very frequently associated with cervical injuries and post-traumatic cervicalgia. Historically, head pain or headache was believed to be reported far less commonly in more severe injuries (77). More recent research suggests that even persons status post moderate to severe traumatic brain injury suffer from acute headache symptoms, most often on a daily basis and in a frontal location and tended to improve with time with recovery generally leveling off by 6 months post-injury (78). The general experience, however, continues to indicate a trend towards greater levels of subjective complaints of headache among those individuals with milder brain injuries as opposed to more severe ones. Zasler (79) has speculated that the primary cause for such headaches is in fact related to cervical injury and that early treatment rendered to persons with more severe TBI, such as chemical paralysis and protracted bedrest, may actually be therapeutically, albeit inadvertently, prophylaxing against the development of PTHA.

Post-traumatic headache and in particular post-concussive headaches seldom connote serious underlying neurological problems. Clinicians should be aware, however, of various significant clinical conditions that may be responsible for PTHA and therefore should always appropriately consider the differential diagnosis of this condition including late intracranial, extra-axial hematomas, tension pneumocephalus due to dural leaks, communicating hydrocephalus, ventriculoperitoneal shunt malfunction resulting in low or high pressure headaches, post-traumatic epilepsy (whether convulsive or non-convulsive) and carotid-cavernous fistulas (80).

There continue to be significant disparities in classification and nomenclature regarding post-traumatic headache (PTH), often because these are arbitrary and not predicated on physiology or established time courses for symptom manifestation (79). The etiology, course, pathophysiology and treatment remain poorly understood (81). The International Headache Society published their revised classification system in 2004 (82). As per the revised classification, there are two broad categories of

headache including acute PTHA and chronic PTHA. Acute PTHA is further divided into headache associated with moderate to severe (5.1.1) and that associated with mild head injury (5.1.2). Chronic PTHA is divided into the following sub-classifications: chronic headache due to moderate to severe head injury (5.2.1) and chronic headache due to mild head injury (5.2.2). There are many consternations regarding this classification and more importantly the specifics of the criteria including onset time, duration of headache, misuse of the modifier “chronic” (which typically is used to modify pain when pain duration is six months or greater), causation criteria, use of “head injury” as opposed to “brain injury”, among other problems. It should be noted that there are further classifications for: acute, as well as, chronic headache attributed to whiplash injury, headache due to traumatic intracranial hematoma, headache associated with other head and/or neck injury, as well as, post-craniotomy headache. Interestingly, there are no specific headache classifications for post-trauma migraine, tension headache or neuritic/neuralgic headache (82).

Potential sources of head pain that may be relevant in the assessment of a patient presenting with post-traumatic headache include the dura, venous sinuses, cranial cavities including sinuses, eye socket, ear, nasal and oral pharynx. The skin, nerves, muscles and periosteum of the cranium are all pain sensitive. Cervical/cranial joint capsules (including the temporomandibular joint), cervical facets/zygapophyseal joints and the cervical sympathetic plexus may all be primary nociceptive pain generators that produce local or referred head pain (83, 84). One of the most common, yet often overlooked, sources of head pain is referred cervical myofascial pain emanating from any of the four layers of posterior cervical musculature secondary to cervical acceleration deceleration injuries generally associated with the traumatic events that caused the brain injury in the first place (85, 86) (see Figures 38-6-9).

**Clinical Evaluation of Post-traumatic headache**

The distinction between various types of post-traumatic headache has become somewhat blurred in the majority of the scientific literature. Defining variables used in various studies may actually overlap headache subtypes. Furthermore, as discussed above, the presence of primary and

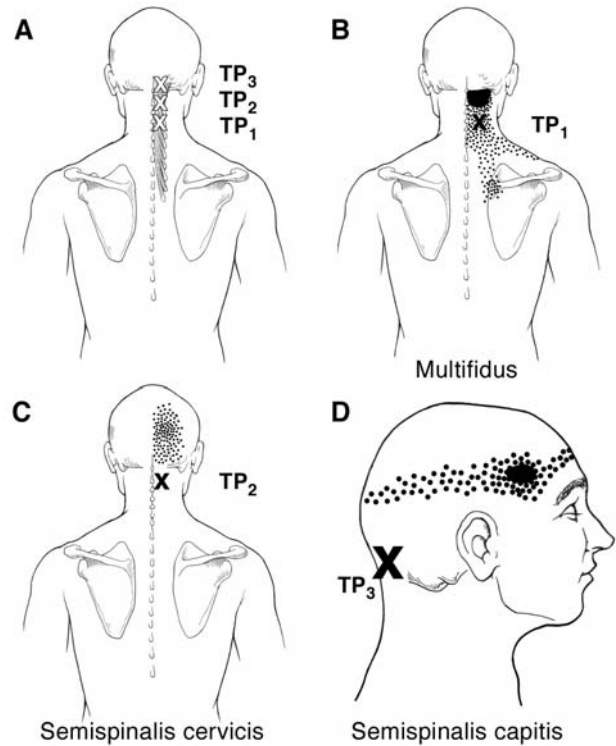


FIGURE 38-7

Posterior cervical muscles prone to development of trigger points producing referred pain perceived as cervicalgia and/or cephalgia

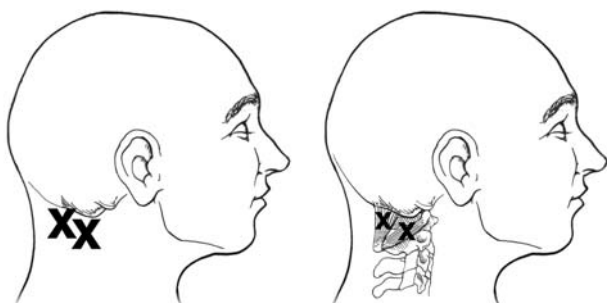


FIGURE 38-6

Sub-occipital muscle trigger points

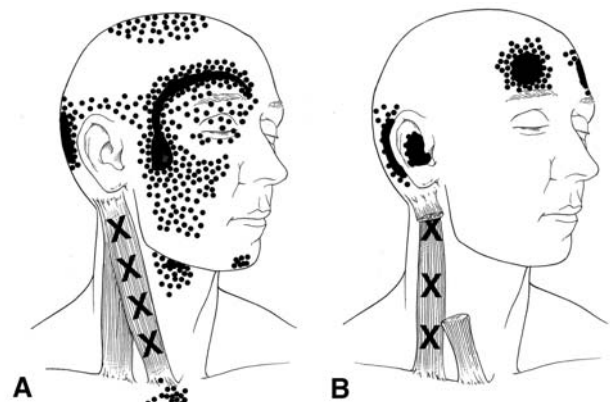


FIGURE 38-8

Referred pain patterns for sternocleidomastoid muscle trigger points, sternal division (A) and clavicular division (B)



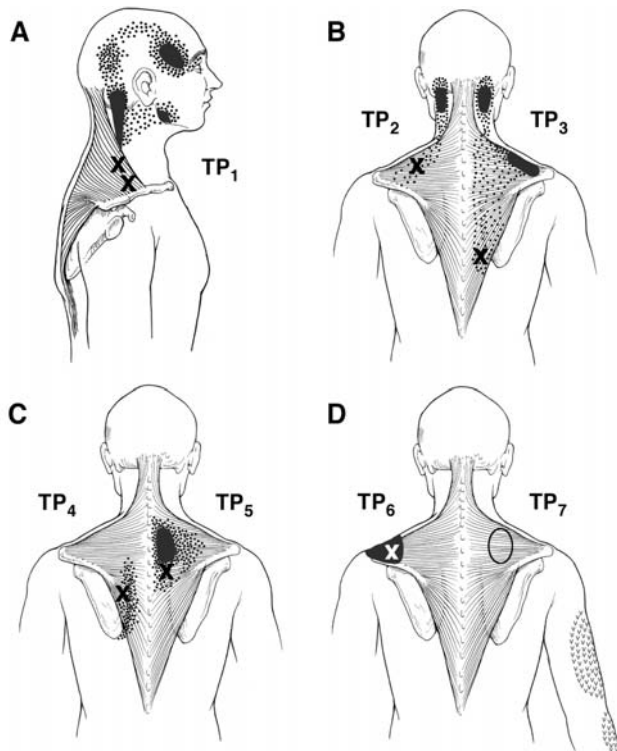


FIGURE 38-9

Trapezius muscle trigger point referral patterns

secondary peripheral sensitization, along with windup and central sensitization, along with the concepts of resulting expanded receptive fields and “convergence-projection” may make the identification of the original nociceptive generator quite difficult. This may indeed be moot, since it may be beneficial to treat both the primary pain generator and the secondary/concurrent pain generators in order to reduce the disabling consequences of post-traumatic headache. It remains important, however, to identify likely sources of pain (primary and secondary) in order to treat them. Readers interested in PTHA should consult more comprehensive treatises for a more complete overview (79, 81).

Historical information regarding mechanism of injury can help distinguish types of headache. The physical forces involved in post-traumatic headache include impact and/or acceleration/deceleration (inertial) loading; the latter typically involves “whiplash” type injury to the neck. In more generalized post-traumatic headache, surgical intervention provides yet another “external physical force” that may produce head pain.

On review of systems, it is useful to use the acronym “COLDER”; Character: dull, throbbing, lancinating, sharp, etc.; Onset: any precipitants, relationship to menses, time of day, temporal relationship to injury; Location: Unilateral, bilateral, occipital, radiating, frontal, bitemporal, etc.; Duration: length of headache

episodes; Exacerbation: stooping, valsalva, bending, touch, stress, poor sleep, menses, weather changes, etc.; Relief: Medications that work, modalities that help, sleep, etc. Other questions that should be asked include the severity of the headache (where 0 is none and 10 is the worst imaginable), frequency of the headache, associated symptoms (nausea, vomiting, photophobia, and/or phonophobia), presence of an aura, as well as the degree of functional disability associated with headache episodes including their vocational impact (e.g. how many days of work missed per month) (84, 80).

The physical examination should include observation (for traumatic changes, asymmetries and general posture), neurological examination, cervical ROM, palpation of cervical and cranial musculature, palpation of GON and LON egress points, provocative movements, ocular examination and auscultation for carotid, mastoid, temporal and ocular bruits. Although an in-depth discussion of myofascial pain is beyond the scope of this chapter, the reader is referred to other more extensive resources (84, 85, 87). Myofascial pain is very common in the sternocleidomastoids and trapezius after whiplash or inertial injury. It is interesting to note that the zone of referred pain for the sternocleidomastoid extends to retro-orbital and periorbital areas; associated “autonomic” symptoms include vertigo, tinnitus, and a sense of fullness in the ear, as well as, ear pain (commonly confused for otitis externa). These symptoms may be explained by convergence projection theory in that there is overlap in the sensory dermatomes for the SCM and the trigeminal tract as discussed above. The cervical musculature is also a major source of afferents to the vestibular systems integrating eye, head and neck movement, thereby making dizziness a common complaint in this patient population (so called cervical vertigo). The zone of referred pain to the ear overlaps the sensory area for the vagus; theoretically, peripheral sensitization in the SCM could lead to central sensitization within the vestibular and possibly vagal systems (80) (See Figures 38-6–9).

### Common Clinical Subtypes and Features of Post-Traumatic Headache

#### *Musculoskeletal Headache*

Musculoskeletal headache is classically characterized as a cap-like discomfort, but varies with the offending musculature. The sternocleidomastoid is notorious for referring pain retro or peri-orbitally. The pain may be constant or intermittent, relieved by application of heat, cold, massage and many over the counter medications including NSAIDs. There may be autonomic components to specific muscles. TMJ or craniomandibular syndrome may be considered a variant of musculoskeletal or tension headache and is almost always seen in conjunction with

direct trauma to the craniomandibular complex when traumatic in origin. This type of headache is also frequently overlooked as a primary or contributory cause for PTH (88). In TMJ, clicking, popping or malocclusion of the jaw may be noticed (89). Other etiologies of TMJD must be assessed for that may have little to nothing to do with the traumatic injury in question, whether in relation to stress or tension, dental malocclusion, and/or prior psychosexual abuse.

Many of the patients with musculoskeletal headache have as a primary or secondary component, myofascial pain. The therapeutic targets are pain relief, stretch to normal length (establish normal range of motion), and then strengthening of the involved musculature. Efforts to correct postural or skeletal problems, as well as, disordered sleep cycles, should be undertaken as well. Pharmacological interventions for myofascial pain include NSAIDs, TCAs and possibly muscle relaxants. TCA's, particularly amitriptyline, may help with disordered sleep. "Muscle relaxants" have no proven efficacy, although some resemble TCA's in their chemical structure and clinical effect. Anti-spasticity drugs are seldom used, although tizanidine may have some theoretical benefit over other traditional anti-spasticity agents due both to selectivity and anti-nociceptive properties. The hallmark of treatment of myofascial pain has been the treatment of trigger points, as well as, promulgating factors (90). These may be approached with acupressure or dry needling, but most practitioners use injections of local anaesthetic, followed by stretch of the involved muscle group and/or physical interventions directed at "myofascial release" techniques (91). Recently, the use of botulinum toxin (off label) has been advocated for modulation of chronic myofascial pain (92). Theoretically, this should allow for increased ability to stretch the muscle, but may impede later phases of treatment related to strengthening. Non-pharmacologic treatment of myofascial pain involves the use of modalities and therapy. Various heating modalities are well tolerated by most patients, and allow for muscle relaxation for therapeutic stretch. Some patients respond well to cooling with fluorimethane spray for the same purposes. Patients should be taught a home program of stretching, and then a gradual strengthening program. Current literature does not strongly support the use of physical treatments per se in the management of headache disorders (93).

Within the broad category of musculoskeletal headache, other etiologies beyond the almost omnipresent myofascial pain include cranio-mandibular syndrome, cervical zygapophyseal joint disorders (see section below on cervicogenic headache), and "cranial and somatic dysfunction." In craniomandibular disorder, there may be internal derangement of the temporomandibular joint and almost always a myofascial component related to muscles of mastication (temporalis, pterygoids, or masseter). These

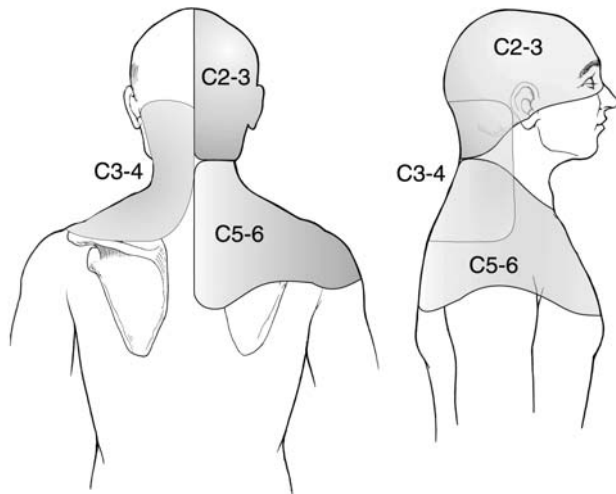
muscular problems should be treated as described above. Often intervention is supplemented by the use of intra-oral appliances such as occlusal splints (bite blocks), dietary changes relative to softer food consistency and jaw exercises. Non-surgical treatment is effective in managing more than 80% of patients with craniomandibular disorders (94). In the case of joint pathology, which may be identified with MRI, arthroscopic intervention is indicated. Open arthrotomy or arthroplasty is rarely needed, and often associated with suboptimal outcomes.

### *Cervicogenic Headache*

Cervicogenic headaches may be related to dysfunction of the facet joints. Others have hypothesized that chronic pain following cervical acceleration-deceleration type injuries may be due to central sensitization (95).

Preliminary diagnostic criteria were developed in 1987 and were consolidated into a formal statement in 1990. Obligatory for the diagnosis were unilateral head pain without side-shift and symptoms or signs of cervical involvement, the latter which could include provocation of pain by neck movement or by external pressure to the upper posterior neck, concurrent cervicgia or reduced cervical range of motion. Subsequent, Sjaastad et al. (96) further amended the criteria by moving the cervical involvement to the first major criteria and relaxing the criterion for unilaterality to the point of even accepting bilateral occurrence. Emphasis to date has been on the nosologic validity of the criteria and no studies have established that patients who meet the diagnostic criteria actually have a cervical source for their pain (97). The IHS criteria of 2004 further refined the diagnostic criteria for cervicogenic headache and included a parameter noting that pain would resolve within three months after successful treatment of the causative disorder or lesion. Most patients present with unilateral (albeit sometimes bilateral) sub-occipital pain as well as secondary oculo-frontotemporal discomfort/pain.

Dysfunction of the cervical zygapophyseal joints, particularly at C2 and C3 may refer pain to the head (see Figure 38-10). Treatment considerations include injection of local anaesthetic intra-articularly, or block of the medial branches of the dorsal rami supplying the joint. At a more subtle level is the concept, which remains somewhat controversial from an allopathic perspective, of cranial and cervical somatic dysfunction. These disorders are typically treated with osteopathic techniques designed to re-align dysfunctional units. Cervical mobilization and manipulation may be effective in the treatment of chronic headaches (98). Various techniques may be used, but caution should be exercised with high velocity procedures due to risk of cervical fracture and/or vertebral artery damage, the latter which is generally avoided by avoiding mobilization in extension.



**FIGURE 38-10**

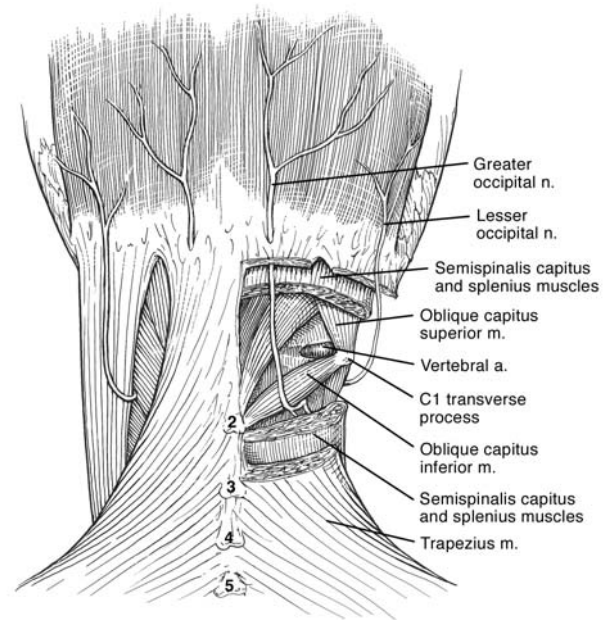
Cervical sensory dermatomes for sensory roots C2-6

Cervicogenic headache is quite common following trauma (99). Some have argued that it is likely the most common etiology of post-traumatic headache (100, 101). Numerous treatments have been assessed, most with sub-optimal study methodologies (102). The studies suggest that in appropriate cases manual therapy (103), exercise and blocks (diagnostic as well as therapeutic) may play important roles in modulating cervicogenic headache pain (97).

#### *Neuritic and Neuralgic Head Pain*

Neuritic scalp pain may occur from local blunt trauma, surgical scalp incision or penetrating scalp injuries. Occasionally, neuromatous lesions may form after scalp nerve injury and serve as a pain nidus. Pain complaints may vary from only report dysesthetic “numbness” discomfort on touching to lacinating type pain that spontaneously occurs without provocative measures. Neuralgic pain may occur secondary to occipital neuralgia (greater and/or lesser), supra-orbital and/or infra-orbital as the most common clinical post-traumatic cephalic and/or facial neuralgias seen in clinical practice although certainly other post-traumatic neuralgias/neuropathies may be observed (104).

Occipital neuralgia (ON) may occur following cervical acceleration deceleration type injuries, as well as, direct trauma to the craniocervical junction. ON may be perpetuated by contraction or myodystonia of the splenius muscle, which it penetrates. Pain is typically felt at the craniocervical junction and the sensory distribution of the nerve (e.g. C2). The affected nerve is tender to palpation and palpation generally replicates the pain associated with the headache (e.g. stabbing quality). There is frequently referral of pain into the ipsilateral frontotemporal scalp



**FIGURE 38-11**

Anatomy of upper posterior cervical region with specific reference to C2 terminal branches of the lesser and greater occipital nerves

and less frequently retro-orbitally (also ipsilaterally) secondary to ephaptic transmission between the proximal part of the C2 origin of the nerve and the ophthalmic branch of the fifth cranial nerve (86).

Whether the etiology is local neuroma formation in scar tissue in the scalp, or greater or lesser occipital neuralgia, the systemic pharmacological interventions are essentially the same and include NSAID's, TCA, and anti-convulsants, particularly, gabapentin. Injection of local anaesthetic with or without steroid may also be indicated for both diagnostic and therapeutic purposes for neuritic and neuralgic pain disorders. For greater and lesser occipital neuralgia, in particular, clinicians should be familiar with the anatomy of the region given risks of aberrantly placed injections (see Figure 38-11). In either situation, myofascial pain may be a secondary or perpetuating pain generator and must be treated as well on a concurrent basis. Rarely, surgical decompression or nerve lysis (surgical, cryotherapy) is necessary for these types of neuropathic cephalalgias.

#### *Post-Traumatic Migraine*

Post-traumatic migraine (PTM) or neurovascular headache is more common than originally thought although its true incidence is poorly defined in the available scientific literature. Patients with PTM may have a genetic predisposition to development of migraine following trauma to either the head/brain and/or neck (105).

There is inadequate information to stipulate how acute PTM may differ mechanistically and otherwise from chronic PTM.

PTM is most likely to be described as throbbing. Vascular headache is usually unilateral and is exacerbated by coughing, bending over; cold may help, but heat usually makes the pain worse. There may be associated nausea, vomiting, or anorexia. Hemicranial allodynia may occur after central sensitization takes place.

The aim of treatment of migraine or neurovascular headache is to prevent or reduce the frequency of the onset of headache (prophylactic treatment) and/or to abort a headache rapidly should it occur (as well as sustain the headache relief once aborted). The precise trigger for migraine or vascular headache remains obscure and controversial; this is especially true in relation to post-traumatic vascular headache. What is clear is that the trigeminal afferent system becomes sensitized by a sterile inflammatory “soup” that includes excitatory neurotransmitters, nitric oxide, histamine, prostaglandin E<sub>2</sub>; this sensitization then produces vasodilatation of extracerebral vessels, including those in the meninges, and accentuates the inflammatory response. The pounding headache of migraine appears to originate from dilatation of large cranial vessels innervated by the trigemino-vascular system and the associated release of CGRP, substance P and neurokinin A from trigeminal neurons; sensitized trigeminal afferents may provide nociceptive input from simple mechanical stimulation of the dilated vessels, akin to a vascular allodynia. Triptans block the release of CGRP at 5HT<sub>1B</sub> and D receptors. However, stimulation of 5HT<sub>2B</sub> receptors promote migraine; TCA’s may block these receptors (106). Second order neurons in the brainstem are sensitized; the periaqueductal gray seems particularly vulnerable in migraine (13).

Prophylactic migraine medications include some NSAIDs, beta-blockers, calcium channel blockers, TCA’s and depakote as more traditional treatments. Naturopathic agents such as butterbar and feverfew can also be considered as can nutritional therapies such as B complex vitamins and magnesium supplementation. Abortive medications may include ergot derivatives, dihydroergotamine derivatives, triptans, parenteral atypical antipsychotics (107) and/or narcotics, among other drugs. However, triptans, as a class, may be ineffective if their use is delayed and allodynia develops (10). Many of the drugs were used for their vasoconstrictive properties (ergot derivatives) even though extra-cerebral vasodilation is a secondary phenomenon in migraine; they have significant systemic or cardiac side effects; If patients experience chronic daily headache and use abortive analgesics, they are at risk for developing rebound or medication overuse headache. Stimulation of various analgesic receptors in the brainstem affects 5HT. Short term use (including acetaminophen) increases 5HT release from raphe spinal

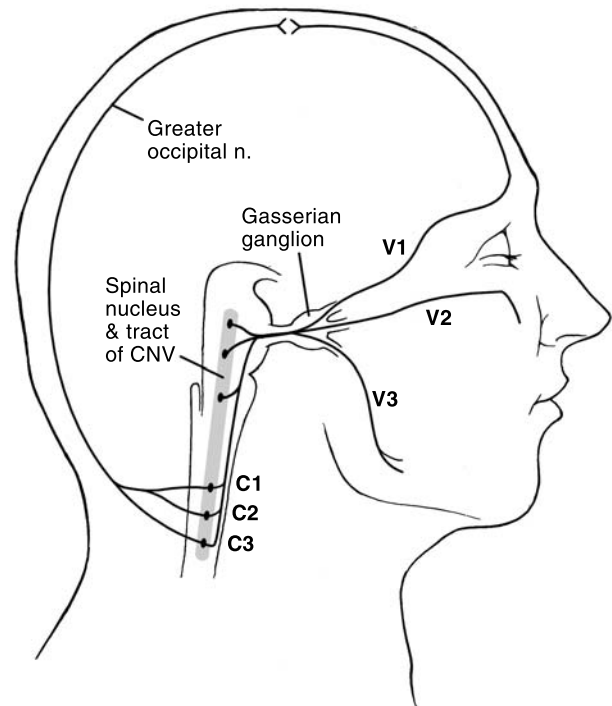


FIGURE 38-12

Schematic representation of interconnectivity between the spinal nucleus and tract of cranial nerve V, upper three cervical roots and the ophthalmic branch of the fifth cranial nerve through the gasserian ganglion

pathways, and has a therapeutic effect. However, long term use may lead to 5HT depletion and up-regulation of 5HT<sub>2A</sub> receptors particularly. Whereas stimulation of 5HT<sub>1b</sub> and 1D receptors aborts acute migraine (e.g. triptans), 5HT<sub>2A</sub> stimulation increases neuronal excitability and potentiates nociceptive transmission. The increased density of 5HT<sub>2A</sub> receptors could lead to an “excitable brain,” a hyperalgesic state, with increased headache frequency and severity. It also undercuts the antagonism of 5HT<sub>2</sub> which is a common mechanism underlying preventative medications in migraine management (22). Caffeine over-use may also contribute to patients becoming refractory to abortive medications containing this substance.

Again, due to central overlap of primary nociceptive afferents involved in true vascular headache and those related to cervical sensory nerves, the patient may present with a combination of vascular, neuralgic, and/or musculoskeletal headache, all of which may require treatment. Cervical nociceptive input may also promulgate migraine through the trigeminocervical complex (108) and therefore must be addressed as part and parcel of comprehensive migraine assessment and treatment (23) (see Figure 38-12).

Botulinum toxin has also been used (off label) to treat migraine headache (109). Botulinum toxin may

exert this effect not only through muscle relaxation but through inhibiting release of sensitizing neurotransmitters such as glutamate and substance P. Current research with botulinum toxin seems to be focusing on specific headache sub-types, specifically, chronic daily headache (110) and not trigeminovascular type headache disorders.

### *Post-Traumatic Tension Headache*

Tension-type headache (TTHA) is one of the most common primary headache disorders and like many other headache conditions can be considered a spectrum disorder. Per ICDH-2 criteria 2.1 to 2.4 diagnostic categories for TTHA include: infrequent episodic TTHA, frequent episodic TTHA, chronic TTHA and probable TTHA (111).

Advances in basic pain and clinical research have improved the understanding of the pathophysiologic mechanisms of tension-type headache. Increased excitability of the central nervous system generated by repetitive and sustained pericranial myofascial input may be responsible for the transformation of episodic tension-type headache into the chronic form. Studies of nitric oxide (NO) mechanisms suggest that NO may play a key role in the pathophysiology of tension-type headache and that the anti-nociceptive effect of nitric oxide synthase inhibitors may become a novel principle in the future treatment of chronic headache (112). It should be noted, however, that other neurochemicals including calcitonin gene-related peptide (CGRP), serotonin, substance P, neuropeptide Y and vasoactive intestinal peptide (VIP) have all been in either episodic and/or chronic TTHA (111).

The mechanisms by which trauma, either to the neck, cranium or cranial adnexal structures or the brain itself may trigger tension type headaches are poorly understood. TTHA may result from an interaction between changes in the descending control of second order trigeminal brain stem nociceptors and interrelated peripheral changes, such as myofascial mediated pain and/or pericranial muscles nociceptive afferent input. Clearly, stress and negative emotional states (mediated through limbic circuitry) may trigger such headaches through central mechanisms; what role TBI itself has in potentially triggering such headaches in susceptible individuals is less clear. With more frequent episodes of headache, central changes have been theorized to become increasingly more important. With greater duration, long term sensitization of nociceptive neurons and decreased activity in the anti-nociceptive system gradually leads to chronic TTHA. Current consensus is that peripheral mechanisms are most likely involved in episodic TTHA and central mechanisms play a more important role in chronic TTHA. There is still debate as to whether the pain in TTHA originates from peripheral (e.g. myofascial) versus central origins.

Treatment of TTHA should include pharmacotherapy, both acute and prophylactic, as well as, non-pharmacologic approaches (111). The mainstay of acute pharmacotherapy are NSAIDs sometimes in conjunction with caffeine, sedatives and/or tranquilizers. Adequate doses of NSAIDs must be utilized prior to labeling a trial as a failure. There is no scientific evidence to support the use of traditional muscle relaxants in TTHA. Prophylactic pharmacotherapy for TTHA is much more diversified with various drug classes being utilized including tricyclic antidepressants, tizanidine, botulinum toxin and certain SNRIs such as venlafaxine (113). Nitric oxide synthase inhibitors may also hold therapeutic promise (114). Non-pharmacological treatments may include relaxation therapy as well as EMG biofeedback, cognitive behavioral therapies including stress management, limited contact treatment, physical therapy when apropos, and lastly, oromandibular treatment in selected patients.

### *Rare Post-Traumatic Headache Subtypes: Dysautonomic Headache, Cluster and Paroxysmal Hemicrania*

Various dysautonomic headaches have been reported and although rare should be considered in the differential diagnostic work-up of a patient with PTHA. Clues to a dysautonomic source of headache pain include a unilateral episodic throbbing pain and hyperactive sympathetics involving the ipsilateral face during the attack (miosis, sweating) but between attacks, a mild Horner's syndrome (115). Trigeminal autonomic headaches have also been reported (116). Post-traumatic cluster headache and paroxysmal hemicrania are relatively rare types of post-traumatic headache (117, 118). It should be noted, however, that with less common headache variants there is always a question about the causal relationship of the injury to the headache onset and promulgation. The literature is scant in proving a causal link between trauma and these headache sub-types.

### *Analgesic Rebound Headache*

Analgesic rebound headache may be seen from overuse of a variety of analgesic and/or abortive headache agents including ergotamines, opiates, caffeine, triptans and/or barbiturates (119). Overuse of these medications may lead to development of chronic daily headache (CDH). Patients may become dependent on these symptomatic headache medications. Drug withdrawal normally results in worsening of headache this is particularly noted when medication is stopped suddenly as opposed to being slowly weaned with concurrent alternative headache management options prescribed. Headache medication overuse may also make headaches refractory to prophylactic headache medication (120).

### *Post-Traumatic Sinus Headache*

Sinus headaches, which may be post-traumatic or unrelated (or both), may be steady or have a throbbing quality. They may be seasonal or associated with allergic symptoms. A history of sinus or facial fractures is relevant. The daily pattern of sinus headaches relates to drainage angles: frontal and ethmoid are often worse with recumbency at night and better during the day when upright, whereas, maxillary and sphenoid sinus headache improves with recumbency at night.

### **Neuropathic Pain**

Neuropathic pain is defined as a chronic pain condition that occurs or persists after a primary lesion or dysfunction of the peripheral or central nervous system. Traumatic injury of peripheral nerves also increases the excitability of nociceptors in and around nerve trunks and involves components released from nerve terminals (neurogenic inflammation) and immunological and vascular components from cells resident within or recruited into the affected area. Action potentials generated in nociceptors and injured nerve fibers release excitatory neurotransmitters at their synaptic terminals such as L-glutamate and substance P and trigger cellular events in the central nervous system that extend over different time frames.

Neuropathic pain has been shown to be mediated by both peripheral and central nervous system phenomena. In the peripheral nervous system mechanisms that have been posited to be involved with neuropathic pain include, but are not necessarily limited to, spontaneous ectopic discharges, neuroimmune factors such as inflammatory cytokines and sympathetic sensory coupling. Central nervous system mechanisms that are theorized to be involved with neuropathic pain include central sensitization, disinhibition, as well as, astrocyte and microglia activation (121).

Short-term alterations of neuronal excitability, reflected for example in rapid changes of neuronal discharge activity, are sensitive to conventional analgesics, and do not commonly involve alterations in activity-dependent gene expression. Novel compounds and new regimens for drug treatment to influence activity-dependent long-term changes in pain transducing and suppressive systems (pain matrix) are emerging. At present, therapeutic options are largely limited to drugs approved for other conditions, including anticonvulsants (carbamazepine, gabapentin, pregabalin), antidepressants (TCAs, venlafaxine, duloxetine), antiarrhythmics (e.g. mexiletine), tramadol and opioid analgesics. However, treatment based on the underlying disease state may be less than optimal, in that two patients with the same neuropathic pain syndrome may have different symptomologies and thus respond differently to the same treatment. Increases

in our understanding of the function of the neurologic system over the last few years have led to new insights into the mechanisms underlying pain symptoms, especially chronic neuropathic pain.

Neurosurgical options may need to be considered when enteral pharmacotherapeutic options fail or produce sub-optimal pain control. Surgical options include modulative techniques, such as neurostimulation or implanted drug delivery systems, and ablative procedures such as DREZotomies (122).

### **Central Pain Syndromes**

Central pain is defined as “pain associated with lesions of the central nervous system.” People with TBI may experience central pain akin to that recognized as post-stroke pain, but may also have associated spinal cord injury with spinal pain. Sixty to seventy percent of patients with SCI have pain that is often chronic in nature (123). Diffuse pain below the level of the lesion may be due to involvement of the posterior spinal tracts, there may be a band-like pain at the transitional zone, or in pain developing late after injury, the source may be a syrinx (124).

Evident from the discussion of the anatomy and neurochemistry of nociceptive transmission, multiple systems contribute to the development of central pain. It is prudent to be cautious in medication and other treatment choices, given the overlap in plasticity mechanisms subserving central sensitization and more positive dynamic neurological functions such as learning, memory and motor recovery. However, it would also be clinically appropriate to consider combinations of medications with different mechanisms of action (whether in the same or different “class” of drug) in an effort to effectively treat the pain syndromes after TBI.

Brain-related central pain develops in about 8% of stroke patients, although its incidence and prevalence following TBI are unclear. It is classically seen with lesions of the thalamus, particularly the ventrocaudal nuclei. Changes in thalamocortical processing may include loss of inhibition or sensitization. Allodynia and dysesthesias, sometimes involving the entire hemispheres are hallmarks of brain-related pain. Central pain syndromes have often been very challenging for both the treating physician and the suffering patient.

Intravenous morphine and intravenous lidocaine may be effective for treatment. Enteral opioid pain medications may be effective but are sometimes poorly tolerated on a chronic treatment basis. Similarly, oral mexiletine does not seem to be as effective as its IV counterpart, lidocaine (125, 126). Tricyclic antidepressants have been used for decades, but caution must be observed in those over 65 because of anticholinergic side effects (127). Anticonvulsants have also been used; there appears to be some effectiveness with lamotrigine in doses of

200–400 mg/day for both brain and spinal cord pain (128). Gabapentin may also be effective (129), but topiramate does not seem to have clinical benefit (130).

Non-pharmacological interventions have also demonstrated benefit in some patients who are refractory to pharmacologic management. Such interventions have included transection of spinal nerves or cordotomy (although 60–80% of patients may have recurrence of pain after 2 years), spinal cord or deep brain stimulation, which appears to enhance GABA transmission (124).

### Complex Regional Pain Syndrome (CRPS)

CRPS remains a much debated clinical condition with perhaps as much misinformation as information (131). The latest research developments suggest that this condition is multidimensional with neuropathic, nociceptive and inflammatory components with associated sympathetic system dysfunction. Current consensus opinion also indicates that CRPS is likely associated with central sensitization phenomena as well as motor abnormalities. Treatments that have been shown to be efficacious include a gamut of physical interventions, pharmacotherapeutic measures, and interventional treatments. Research has suggested that interdisciplinary programs emphasizing functional restoration may offer the optimal treatment paradigm. As noted by Harden (132), “Functional restoration should provide different interventional and non-interventional modalities in a timely manner to facilitate reanimation and normalization of use and movement of the affected limb”. Pharmacotherapeutic interventions for pain can be considered as either “maintenance” or “rescue/abortive” and include such diverse drug classes as tricyclic antidepressants, opioids, anticonvulsants, NSAIDs, clonidine, nifedipine, alpha-adrenergic antagonists (e.g. phenoxybenzamine and phentolamine), bisphosphonates, calcitonin, among the most well studied (132). Interventional treatments that have shown benefit include both sympathetic and epidural blocks.

### Conclusion

Pain clearly is a complex clinical phenomena (133, 134). Treatment of post-traumatic pain conditions is even more multidimensional, whether in the acute or chronic phase post-injury. Judicious use of medical interventions must rely not only on sound medical knowledge that remains up to date with current accepted practice but also on keen observational, interview and examination skills. A sound familiarity with the post-traumatic pain literature, as well as, the myriad conditions that can be seen following multi-trauma and/or traumatic brain injury (135) is paramount to recognizing these clinical conditions when they present themselves. As was once said by Goethe, “We see what we look for, we look for what we know”.

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# 39

## Psychological Approaches to Comprehensive Pain Assessment and Management Following TBI

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### INTRODUCTION

The purpose of this chapter is to help illustrate the important components and increase awareness and understanding of psychological approaches to assessment and management of pain in persons with TBI. This illustration is intended to assist with the making of appropriate referrals, and promoting effective carryover and integration of pain management principles into care of persons with concomitant TBI. It is not intended as a substitute for the necessary training and experience that is prerequisite to providing effective assessment and treatment of pain in persons with TBI.

#### **A Brief Overview of Pain: An Informed Conceptualization**

Pain is defined by the International Association for the Study of Pain (1) as a “psychological state” characterized by “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” An important distinction, with associated differences in definition, pathophysiology, phenomenological experience, plus assessment and treatment focus, relates to chronicity. Acute pain, usually occurring in response to identifiable tissue damage or a noxious event, has more clearly identifiable triggers and neuroanatomical pathways, and

communicates useful information that provokes adaptive responses. It has a time-limited course during which treatment is aimed at providing relief as well as promoting resolution or correction of underlying pathophysiological processes.

As time passes without resolution of an acute pain problem, subjective components may become more pronounced, identifiable triggers and neuroanatomic pathways can become obscure, and behavioral responses can become more disproportionate to underlying pathophysiology and even obstructive to resolution and adaptation. Chronic pain, simply defined as pain persisting beyond six months, may or may not be associated with any obvious tissue damage or pathological process, but can disrupt virtually all life areas and produce marked emotional and behavioral changes. Frequent concomitants of chronic pain include: maladaptive protective responses or pain behaviors; protracted courses of medication use and minimally effective or even iatrogenic medical services; and marked behavioral or emotional changes, including restrictions in daily activities. Pain related avoidance behaviors and reduced activity are likely to result in a cyclic disability-enhancing pattern. The longer pain persists, the more recalcitrant it becomes and the more treatment goals focus on improved coping with pain and its concomitants (2, 3). Finally, there is acceptance that persistent pain is often associated with peripheral or central sensitization effects in which hyper-responsiveness or

spontaneous discharge of components of the pain system develops (4, 5). Numerous functional imaging studies have begun to document the interaction of psychological and neurobiologic processes in chronic pain patients (6–13).

Pain is best conceptualized as a multidimensional subjective experience mediated by emotion, attitudes and other perceptual influences. Variability in pain responses is the rule rather than the exception and appears to reflect complex biopsychosocial interactions between genetic, developmental, cultural, environmental, and psychological and injury/illness related factors (14, 15). Important distinctions between pain and suffering (16), sensory and affective experience, and impairment and disability (17) (WHO) reflect the variability in response to pain problems. While some pain patients appear to present with unusual and possibly exaggerated suffering or disability, others present with a kind of “la belle indifférence” in which extremely high reported pain severity may be associated with no apparent affective distress, pain behavior or interference in many life activities. In some cases, the onset, maintenance, severity or exacerbation of pain is primarily associated with psychological factors and may warrant a DSM-IV (18) diagnosis of Pain Disorder Associated with Psychological Factors. In this regard, it has been noted that there is an association between post-traumatic stress reactions and development of chronic pain (19–22), with uncontrollable pain following physical injury potentially representing the core-trauma resulting in post-traumatic symptomatology (23). However, it is cautioned that one should avoid the pitfalls of mind-body dualism and always consider both psychological and organic factors in the presentation of any chronic pain patient (24).

It should be emphasized that pain may arise from a combination of numerous physical and psychological factors. Complexities in pain presentation warrant referral to pain management specialists and/or specialty interdisciplinary pain programs (25). This is particularly true in cases of “intractable” and functionally disabling pain. It is always best to intervene when “pre-chronic”, where competent, specialized, early intervention offers the greatest hope of facilitating adaptation.

The importance of assessing and managing pain has been incorporated into the prevailing standards of health-care practice in the United States. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO), in its recent accreditation manuals, acknowledges that while pain coexists with a number of diseases and injuries, it requires explicit attention (JCAHO, 2000). Overall, the standards require organizations to: 1) recognize individual’s rights to appropriate pain assessment and management; 2) identify persons with pain in initial and ongoing assessments; and 3) educate patients, residents, clients and families about pain management.

### **Traumatic Brain Injury and Pain**

There is a very high comorbidity of chronic pain problems with cranial trauma whether or not there is traumatic brain injury (TBI). Indeed, headache is the primary complaint in virtually all surveys of the post-concussive syndrome (26). The frequency of post traumatic headache (PTH) in the immediate post-accident period has been estimated to be as high as 90%, with problems continuing beyond six months in as many as 44% (3), although there is generally poor understanding of the incidence, etiology or many other aspects of PTH (27).

In addition to headache, many other pain problems may follow trauma, including neck and back pain, complex regional pain syndrome, and fibromyalgia, among others. Curiously, most studies report that pain problems are much more common in less severe as compared with more severe TBI (3, 26, 28) although pain problems may also be common in the latter (29). Importantly, more severe brain injuries may result in reduced sensitivity to pain due to lesions of the CNS structures involved in processing pain, as observed in some dementias (4, 30). Those with more severe TBI may also enjoy optimal post traumatic healing due to reduced activity and extended rest periods (31). In contrast, it has also been suggested that there is increased likelihood for developing a central sensitization or neurosensitization effect (20, 26) after milder injuries, where there is not only no damage to CNS pain processing structures, but less time for healing and rest before return to usual activities with greater opportunity for psychophysiological arousal.

### **Traumatic Brain Injury, Pain, and Neuropsychological Function**

There is increasing awareness of the role that pain may play in symptom presentation following traumatic brain injury, especially with regard to cognitive complaints. Several recent reviews (3, 24, 26, 31–36) have examined literature objectively assessing these complaints. The available evidence strongly supports the conclusion that chronic pain, especially head pain and neck pain, and pain related symptomatology, independent of TBI or neurologic disorder, can and often do produce impairment of cognitive functioning. Multiple lines of evidence, including studies of acute and chronic pain, animal and human studies, experimental and clinical studies and neurophysiologic studies support this conclusion. A brief summary of the converging evidence that supports this conclusion, based on a review by (37) Dr. Martelli, is presented in Table 39-1. Notably, attentional capacity, processing speed, memory, and executive functions, as assessed on neuropsychological tests, are the cognitive domains most likely to be affected.

**TABLE 39-1**  
*Evidence of Negative Effects of Pain on Cognition in Animals and Humans*

1. Experimental animal and human information processing / attentional capacity literature indicates that distracters less aversive than pain disrupt attention, as does pain;
2. Experimental rodent and other mammalian studies showing pain related disrupted maze and other learning for both appetitive (e.g, food reward) and avoidant (eg, shock) stimuli;
3. Experimental rodent studies showing improved performance with cessation of pain;
4. Experimental rodent and other mammalian studies showing improved performance after administration of pain relieving medications known to disrupt cognition;
5. Experimental human studies showing improved cognitive performance after discontinuation of pain stimulus and/ or administration of psychoactive opioid pain relievers;
6. Animal studies showing that stress (including chronic pain) is associated with damage to the hippocampus, inhibition of neurogenesis, and deficits in hippocampal-based memory function;
7. PTSD findings of deficits in hippocampal-based declarative verbal memory associated with smaller hippocampal volume;
8. Recent preclinical evidence showing that selective serotonin reuptake inhibitor (SSRI) antidepressants promote neurogenesis, reverse effects of stress on hippocampal atrophy, improve cognitive deficits observed in OCD, depression, etc;
9. A majority of studies indicating pain cognitive interference effects, at least attention dysregulation, in chronic and acute pain patients. Study designs including experimental pain, neuropathic pain, neurophysiologic measures, combination neuropsychologic and neurophysiologic measures, and reward designs helped to bolster conclusions about interference effects despite failure of most studies to utilize explicit response bias detection measures for pain and cognition.
10. Consistent neurophysiologic studies showing very specific neurophysiologic (e.g. anterior cingulate cortex (ACC)) effects associated with chronic pain and attentional disruption, often co-existing with other patterns, consistent with other disorders also having reasonable evidence of cognitive impairments and neurophysiologic expressions (e.g., hypofrontality and depression);
11. Neural plasticity / cerebral reorganization associated with chronic pain showing functional cerebral changes (e.g. studies showing expansion of sensory cortex (e.g., Flor (11)));
12. Neuroendocrine and HPA perturbation in chronic pain and evidence that pain and chronic stress (and depression) are linked via chronic stress-induced HPA dysfunction (along with evidence of combined muscle energy depletion and serotonin deficiency (peripherally, but also centrally), along with depressed levels of somatomedin C, caused by deficit of stage 4 sleep dependent release of GH, and elevated NE response levels in fibromyalgia;
13. Amassing neurophysiologic evidence of central sensitization (38) and disrupted pain inhibitory mechanisms associated with dysfunctional ACC functioning of both anterior / ventral and posterior/ dorsal quadrants (associated with cognitive and affective regulation, respectively), plus evidence that less severe and less disruptive chronic pain is associated with a greater habituation response to painful stimuli (vs. sensitization) and not associated with cognitive disruption. The newest integration of these findings link a biopsychosocial model where genetics, learning history and psychological variables interact, with a clear role played by anxiety and avoidance conditioning to produce a pattern of pain arousal that mimics OCD, chronic or severe depression, PTSD or high trait anxiety, with hypoaroused inhibition (ACG hypofunction) of pain, obsessional thoughts, anxiety, somatic concerns, intrusive associations/ memories) and disrupted allocation of attentional resources;
14. Evidence that the concomitants of chronic pain alone may account for cognitive disruption; sleep disturbance / deprivation (e.g., metaanalytic studies showing impaired attention and psychomotor function, including greater impairment compared to alcohol intoxication; studies indicating significant trait-like interindividual variability in sleep deprivation effects that are stable within individuals); pain medications; depression and anxiety; and suggestion that combinations are additive;
15. Consistent findings showing both normalization of neuropathophysiology and cognitive function (for performance and self reported improvements in cognition) after effective pain reduction interventions.
16. Indications that chronic pain, as well as depression, are associated with structural cerebral changes. For example, chronic pain has been associated with decreased prefrontal and thalamic gray matter density compared with matched controls, suggesting that the pathophysiology of chronic pain includes thalamocortical processes.

Adapted from Martelli (37).

These reviews indicate that the concomitants of chronic pain may be as important or more important than pain itself in producing cognitive impairment. Specifically, cognitive impairment in chronic pain patients has been associated with mood change/emotional distress, somatic preoccupation and pain catastrophization, sleep disturbance, fatigue, and perceived interference with daily activities that are potential sources of chronic stress. For example, major depression is frequently found following mild TBI, is associated with higher postconcussion symptom endorsement, poor functional outcome, high distress levels, disability and cognitive impairment which typically remit after effective treatment for depression (39). In a metaanalytic review, (40) Pilcher and Huffcutt found that partial sleep deprivation impairs cognitive and motor performance. More interestingly, in a review of experimental human and animal studies, (41) Kundermann, Krieg, Schreiber and Lautenbacher found that sleep deprivation produces hyperalgesic changes and can counteract analgesic medication effects via disruption of both serotonergic and opioidergic processes.

Mahmood et al. (30) examined the previously observed association between sleep disturbance, cognitive and pain complaints and TBI (e.g., Beetar, Guilmette, Sparadeo, (42)). They noted that, while severe TBI is more likely to produce subcortical damage and reduce pain experience, mild TBI is associated with increased pain and sleep disturbance, and that sleep disturbance is associated with frontal hypoactivation that, especially when associated with depression, may render post TBI individual especially vulnerable to cognitive dysfunction. They observed that measures sensitive to executive functioning and information processing speed were associated with sleep quality scores. Consistent with these findings, Mooney et al.'s (39) review of poor recovery following mild TBI found that most of the variance in recovery of mild TBI compensation seekers seems to be explained by depression, pain and response bias versus brain injury variables.

Importantly, these associated factors have consistently been found to be more strongly associated with both cognitive complaints and impairments than is pain severity, although problems with the assessment of pain severity (e.g., response biases to report pain and the restricted range of measurements) may account for the relatively weak predictive power of pain severity ratings. Further, metaanalytic studies and increasing recent evidence have associated these individual factors with decrements in cognitive functioning, independent of chronic pain or combination effects (24, 26, 32–34, 36).

Hart, Wade & Martelli (34) reviewed studies of cognitive functioning in patients with chronic pain with an emphasis on the role of emotional distress and the mechanisms of stress-related effects. The association between psychological distress and cognitive impairment was found to be especially significant for pain-related

negative emotions and variables that mediate suffering, such as interference with activities and increased somatic vigilance. This relationship was independent of the effects of pain intensity. It was noted that the anterior cingulate cortex (ACC) plays an important role in pain processing, attention and affective-motivational experience, and that the ACC appears to mediate the impact of pain-related emotional distress on cognitive functioning through allocation of attentional resources. Further, maladaptive physiologic stress responses and dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis can produce negative effects on hippocampal function and memory. The underlying mechanism for cognitive impairment that Hart et al. (34) postulated is the anticipation of unpredictable pain symptoms, especially in individuals high in trait neuroticism. This presents a significant stressor that repeatedly activates both the HPA axis and ACC areas and results in disruption of cognitive efficiency. Hart et al. (34) did not address what remains a potentially important research area, i.e., how these putative mechanisms might interact in cases of persons with brain injury where neurologic impairments and additional sources of stress are operative.

Clearly, chronic pain and associated problems can complicate the symptom picture in TBI. Especially in cases of persistent sequelae following mild TBI, increasing evidence suggests that chronic head and other pain and associated problems can present a differential diagnostic challenge, and contribute to or maintain symptoms. This evidence provides strong support for the argument that resolution of the post concussive syndrome and successful adaptation to residual sequelae frequently relies on successful coping with post traumatic pain and/or other pain and associated symptomatology. In addition, careful consideration of pain in the differential diagnosis of brain injury is required. Some recommended procedures for conducting neuropsychological assessment of persons when pain is a significant complaint have been included in Table 39-2.

## PAIN ASSESSMENT

Pain is a complex and subjective perceptual process comprised of behavioral, affective, cognitive, and sensory components. Especially when chronic, it often has no clear cut objective pathophysiological correlates. The complexity of this subjective and multidimensional experience is highlighted by independent replicated functional imaging studies showing that anticipation of pain produces similar activation of cortical networks as does pain itself (7, 12, 43). Dualistic (i.e., organic/biologic versus functional/psychologic) models that explain disease and health primarily in terms of measurable biomedical variables have generally not proven useful for measuring or

**TABLE 39-2**  
***Recommendations for Assessing and Minimizing the Confounding Effects of Pain During Neurocognitive Examination***

1. Always assess pain when present, when post traumatic adaptation seems compromised by pain and related symptomatology, or limitations in daily functioning, and decrements in test performance seem atypical. Clarify the frequency, intensity and character of pain during the examination and more generally, the characteristics of the chronic pain experience and related problems.
2. Assess problems that are commonly associated with chronic pain (e.g., sleep disturbance, fatigue, somatic preoccupation, anxiety, depression) as these all have the potential to markedly disrupt aspects of cognitive functioning.
3. Repeat administration of measures sensitive to the effects of fatigue (e.g., sustained, attention-demanding, timed tests) during examinations to help identify or corroborate fatigue-related deficits.
4. Always assess effort, motivation and response bias during examination, especially with regard to symptom complaints.
5. Consider postponing cognitive assessment in cases where pain and related symptomatology have not been appropriately or aggressively treated.
6. Use accommodating? procedures during examinations where possible (e.g., optimizing comfort, providing frequent breaks, allowing frequent position changes and use of personal orthotics [cushions, heating or ice pads, etc.], modifying lighting and sound, etc.).

treating pain. Biopsychosocial models better explain variability in health care outcomes and direct more effective interventions for challenging chronic health care situations, including chronic pain rehabilitation (44).

A biopsychosocial stress and coping formulation conceptualizes adaptation to injury as a series of stressful demands which require interactions between existing coping resources and injury related stresses and demands. Hence, identification of coping liabilities is an integral prerequisite to bolstering coping resources and improving long term adaptation. A biopsychosocial assessment perspective affords the optimal understanding of the patient with pain and the myriad of factors that might contribute to this subjective experience and complicate, or otherwise affect symptom presentation (45). Such factors include not only the patient's medical findings, but also physiological, behavioral, and cognitive-affective functioning, including vulnerabilities and strengths.

A comprehensive, biopsychosocial assessment should be considered the standard of care when pain is chronic (46, 47). Initial assessment should address self report, via interview of patient and relevant others, and use of appropriate assessment instruments, in the following areas:

1. Pain intensity
2. Affective response
3. Quality / characteristics, and
4. Location.

History from the patient regarding the presentation of the pain problem is as important as examination results, and should include inquiry about such questions as: onset and course (e.g., when, where, how; sudden or progressive, fluctuating or steady, etc.), intensity level,

duration, activities preceding an exacerbation, stress related effects, variability across the day and night, effect of movement and posture change, irritating and relieving factors, medications employed and effects, current activities and pain related activity changes, specific effect of pain on mood, activity, cognition, affect, sleep, appetite, and more general effects of pain in the persons life. Importantly, special assessment procedures are indicated in cases of persons with response limitations or significant cognitive impairments. These include special versions of instruments and reliance on observation and structured interview of relevant others and observers, and integration of this information with physical examination procedures (see Hadjistavropoulos, von Baeyer, and Craig (48), for an extensive review of self-report, observational and physiological measures used in pain assessment of adults with impaired communication abilities).

A comprehensive assessment should also address the following areas:

5. Pain behaviors and environmental effects / responses
6. Beliefs about the pain condition
7. Coping strategies and effectiveness
8. Psychosocial context and social responses to pain,
9. Personality and psychoemotional status and adjustment, including how this affects or is affected by pain, and
10. Activity, level of function / disability and quality of life.

A brief survey of general classes and useful instruments for inclusion in a comprehensive pain assessment, updated from previous work (49) is included in Table 39-3. Also included in this table are special instruments designed for persons with significant response limitations and/or cognitive impairment, including the very young and elderly.



**TABLE 39-3**  
**General Classes and Instruments Commonly Included in an Assessment of Pain and Psychological Variables Relevant to Adjustment and Coping**

**Specific Pain Domain Instruments: Self Reported Pain Intensity and Location**

- *Visual Analogue Pain Scale* (VAS (1)): is a brief graphical, nonpsychometric measure of subjective pain intensity represented by a straight line with typical endpoints of no pain and worst possible pain. It is widely used to quickly assess pain report, track changes during treatment, and assess outcome (50).
- *Verbal Rating Scale* (VRS) is a similar measure where pain intensity is indicated on a linear scale with verbal anchors ranging from no pain to worst possible pain and including mild, moderate, severe and very severe (50, 51).
- *Numeric Rating Scale* (NRS) is another similar measure where pain intensity is indicated verbally or by pointing at a number from 0 or 1 to 10 (50, 52).
- *Pain Drawing* ((53, 54)) is a measure of the location aspect of pain. It is the most common instrument used for this type of self-report (50).
- *McGill Pain Questionnaire*, short form (SF-MPQ: (55)) was designed to measure descriptive aspects of pain via selection of adjectival pain descriptors. It provides three classes of pain descriptors: Sensory (burning, sharp, sore), Affective (e.g., exhausting, punishing), and Intensity (e.g., intense, excruciating). Different combination of descriptors may be associated with different nociceptive or psychological factors.
- *Pain Diaries* are temporal measures of frequency, duration and intensity of pain episodes (56, 57). They typically ask subjects to self-report, in a journal for several days or weeks, when and in what situations pain increases or decreases. More complete versions typically assess such areas as: location, intensity, onset (e.g., sudden or progressive; fluctuating or steady, etc.), characteristics (e.g., throbbing, dull aching), duration, preceding activities, stress, effects of pain on activities, cognition, affect, sleep, appetite, and factors affecting pain mitigation or exacerbation (e.g., weather, activity, stress, medications, distraction).

**Instruments Designed for Children and Adults with Significant Cognitive Impairment**

- *FACES Scale* (51) was designed for young children and consists of six cartoon faces ranging from a smiling face for “no pain” to a tearful face for “worst pain”. Versions have been adapted for cognitively impaired adults.
- *Oucher Scale* (58) consists of sequenced pictures of a child’s face, ranging from “no hurt” to “the biggest hurt you could ever have”, which are shown and explained to a child who selects which exemplifies current pain level. It is designed for children and can be used with adults with significant cognitive problems (59). Versions are available for most ethnicities.
- *FLACC* (FACE, LEGS, ACTIVITY, CRY, CONSOLABILITY) Scale is a standardized rating composite measure of observed physical indicators of pain in infants and preverbal children who are unable to provide verbal report. It can also be used in children and adults with severe cognitive impairments (see McGrath and Gillespie (60)).
- *Observational Pain Scale* (61) is a standardized rating measure for estimating pain level in cognitively impaired patients who can’t respond to VAS, Numeric or Oucher Scales. It produces a composite pain score based on observation of: facial expressions, verbalizations/ vocalizations and body movements; changes in interpersonal interactions; changes in activity patterns or routines; changes in mental status; and/or physiologic changes.

**Pain Specific Measures of Functioning: Pain Quality, Affect and Behavioral, Cognitive/ Attitudinal and Emotional Coping**

- *Multidimensional Pain Inventory* (62) employs a biopsychosocial conceptualization to assess relevant psychosocial, cognitive, and behavioral aspects of responses to pain. This well researched instrument has 61 items, includes 13 scales and measures pain severity, patient-perceived pain interference, affective distress, life control, social support, response from others, and disability. It includes specific norms for different statistically derived chronic pain subtypes (63): interpersonally distressed with inadequate social support; globally dysfunctional coping; and adaptive coping. An inexpensive software scoring program is available (64). This multiaxial classification system is a psychometrically sound and objective method of evaluating chronic pain patients, may be integrated with useful psychological information from multiple other sources, and offers benefit for matching patients to types of pain management interventions. In a recent study (65) the MPI successfully classified chronic whiplash associated disorders into homogenous subgroups
- *Pain Affect Visual Analogue Scale* (VAS) can also be used to quickly assess affective pain distress (52) versus sensory intensity, and similarly offers utility for assessing treatment changes and outcome.
- *Pain Patient Profile* (P3) (66) is a screening measure for depression, anxiety, & excessive somatization in pain patients. It is a double normed (both healthy controls and chronic pain patients) screening test developed to measure psychological factors related to chronic pain conditions in order to help identify those who would likely benefit from mental health treatment as part of their treatment plan.
- *Battery for Health Improvement* (BHI) assessment (68) is a dual normed (community samples and pain patients) instrument designed for multidimensional assessment and computerized progress tracking to identify affective,

TABLE 39-3 (continued)

characterological, psychophysiological and social factors that affect pain, recovery and rehabilitation progress, vocational training or job placement readiness, and impairment and disability. It can contribute useful information regarding psychosocial factors underlying pain reports, perceived disability, somatic preoccupation, design for interventions and outcome. A recent revision, the BHI-2, offers expanded national norms and multiple reference groups, along with expanded and updated scales.

- *Profile of Chronic Pain: Screen* (PCP:S:) (68) is a brief 15-item measure designed to identify individuals who merit more detailed psychosocial evaluation. It assesses the psychological impact of chronic pain in terms of: pain severity, functional interference, and pain-related emotional burden. Random national sample data were employed to demonstrate good validity and minimal social desirability response. National norms are available by gender for three age groups.
- *Profile of Chronic Pain: Extended Assessment Battery* (PCP:EA) (69) is a very new, 86-item instrument with: (a) 33 items assessing pain location and severity, pain characteristics (e.g. worst daily pain), medication use, health care status, the identity of the most important person in the patient's life, and functional limitations in 10 areas of daily living; (b) 13 multi-item subscales addressing aspects of coping (guarding, ignoring, task persistence, and positive self-talk), catastrophizing, pain attitudes and beliefs (including disability beliefs, belief in a medical cure for pain, belief in pain control, and pain-induced fear), and positive (tangible and emotional) and negative (insensitivity and impatience) social responses. National stratified samples across three age groups, two survey studies providing strong evidence for the hypothesized factor structure, internal consistency, independence from response bias, and validity, and the presence of normative data suggest good diagnostic and prescriptive utility.
- *Pain Stages of Change Questionnaire* (PSOCQ) (70, 71) has good demonstrated reliability and validity in predicting patient readiness to adopt new beliefs and coping responses to pain. More recent research (72, 73) suggests some utility in identifying patient cluster types that differentially respond to specific multidisciplinary or cognitive-behavioral pain treatments consistent with a self-management approach to chronic pain problems.
- *Survey of Pain Attitudes* (SOPA-R-35:(74)) is a well-researched instrument that assesses patient feelings about pain control, solicitude (solicitous responses from others in response to one's pain), medication (as appropriate treatment for pain), pain-related disability, pain and emotions (the interaction between emotions and pain), medical cures for pain, and pain-related harm (pain as an indicator of physical damage or harm)
- *Pain Catastrophizing Scale* (PCS;(75)) is a brief, well-researched measure of the negative mental set in the presence, or anticipation of pain marked by magnification, rumination and helplessness. Pain catastrophizing is a robust predictor of analgesic use, distress, psychosocial dysfunction, & disability, and superior in comparisons to disease severity, pain levels, age, sex, depression, or anxiety. It also demonstrates benefit as a therapeutic measure of cognitive restructuring as a therapeutic tool (76). A child version is also available (77).
- *Pain Anxiety Symptoms Scale* (PASS) (78) is a measure of fear of pain across cognitive, overt behavioral and physiological domains. It has good correlations with related measures of anxiety and disability and has been found to predict disability and interference due to pain when controlling for emotional distress and pain.
- *Kinesiophobia Scale* (K-Scale:(79)) is a quick screening measure of unreasonable or irrational fear of pain and painful reinjury upon physical movement. It assesses pain-phobias or avoidance conditioned pain related disability (i.e., unhealthy pain maintaining habits that are a major contributor to pain related disability) and correlates highly with similar measures. High scores, once malingering factors are ruled out, signal the need for combination therapies with emphasis on reeducation, countering maladaptive phobic responses and promoting adaptive attitudes and treatment participation/ cooperation (e.g., graduated exposure, cognitive reinterpretation and systematic desensitization). Recently, a version has been adapted for use in the general population (80).
- *Cogniphobia Scale* (C-Scale) (81), adapted from the K-Scale, quickly screens unreasonable or irrational fear of headache or painful reinjury upon cognitive effort / exertion. The C-Scale is designed to assess anxiety based avoidant behavior with regard to cognitive exertion. Like the Kinesiophobia scale, this instrument measures anxiety based avoidant behavior and offers information about need for combination therapies that include such anxiety reduction procedures.
- *Chronic Pain Coping Inventory* (CPCI:(82)) is a 65-item measure of strategies used by patients to cope with chronic pain across 11 pain coping dimensions. In cross validation studies, four scales (Guarding, Resting, Asking for Assistance, and Task Persistence) reliably predicted patient- and significant other-reported patient adjustment. Eight scales (Guarding, Opioid Medication Use, NSAID Use, Sedative-Hypnotic Medication Use, Resting, Asking for Assistance, and Exercise/ Stretch) demonstrated moderate-to-strong consistency between patient and significant-other versions.
- *Chronic Pain Acceptance Questionnaire* (CPAQ) (83) and a revised version (84) is a measure of acceptance of pain. The 20-item revised form has 2 empirically derived subscales: Activity Engagement (i.e., degree to which respondents are living a normal life despite pain) and Pain Willingness (i.e., degree to which respondents have pain experiences without avoidance or control efforts). In a very recent large sample (85) the CPAQ scales were reliably stronger predictors of distress and disability compared with coping variables, suggesting that a pain management efforts can benefit from shaping a more accommodating view of pain experience for certain individuals or circumstances.

TABLE 39-3 (continued)

- *Psychosocial Pain Inventory* (PPI:) (86) is a 25-item, eight-page structured interview designed to assess the influence of psychosocial factors in chronic pain syndromes in 10 areas: 1) pain behavior (e.g., up time, time in bed), 2) social reinforcement, 3) life changes, 4) litigation, 5) financial status, 6) use of alcohol, 7) medication use, 8) coping strategies, 9) social environment, and 10) environmental stress. It also includes questions concerning personal and family histories, past and current medical histories, and reactions and adjustments to the pain and medical treatments.
- *Hendler Chronic Pain Screening Test* (87) assesses contribution of physical versus psychological variables to pain behavior. Higher scores reflect strong psychologically influenced or motivated pain behavior, and suggest recommendations for conservative treatments with multimodality treatment programs. Very high scores typically require further psychological or psychiatric intervention.
- *Headache Disability Rating* procedure of Packard and Ham (88) is a scale that estimates impairment from headache rated on frequency, severity and duration of attacks and how activities impact on functional skills and activities of daily living. Importantly, it includes a modifier variable for rating motivation (i.e., treatment motivation, exaggeration/over concern, and legal interest) that are used to adjust the total impairment rating.
- *Pain Assessment Battery – Research Edition* (PAB) (89): four measures that provide information regarding patient stress, pain reports with qualitative pain analysis and pain coping strategies, including nonorganic pain complaints. Format allows serial computerized administrations and tracking.
- *Oswestry Low Back Pain Disability Questionnaire* (90) assesses the amount of restriction pain imposes on functional levels. Assessment areas include intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and traveling. The percentage of endorsed items gives an indication of the amount of disability. It has been proposed that up to 20% indicates minimal disability, 20 to 40% indicated moderate disability, 40 to 60% indicates severe disability, and greater than 60% indicates severe disability.
- *Vanderbilt Pain Management Inventory* (91) measures chronic pain coping strategies (e.g., active, passive) and provides useful information for treatment planning and recommendations
- *Cognitive Coping Strategies Inventory* (92) assesses the degree to which patients engage in adaptive and maladaptive cognitive coping strategies.
- *Coping Strategies Questionnaire* (64) is a 48-item scale that rates the frequency of engagement in 8 different behavioral and cognitive coping strategies in response to pain or physical symptom experience.

#### **Measures of General Health Functioning and Behavior**

- *Millon Behavioral Health Inventory* (MBHI) and its recent upgrade, the *Millon Behavioral Medicine Diagnostic test* (MBMD) (93) is one of the most frequently used health inventories for medical populations in the US. The MBHI provides information across four broad categories: basic coping styles, psychogenic attitudes, specific disease syndromes, and prognostic indices. It has good psychometric properties, a large normative database of representative medical patients, with specific disease scales developed for specific patient groups. The MBMD has updated and expanded the research base and clinical scales (165-items, 38 scales, 3 validity scales). The MBMD assists with: identification of significant psychiatric problems, making specific recommendations; pinpointing personal and social assets to facilitate adjustment; identifying medical regimen compliance problems; structuring post-treatment plans and self-care responsibilities in the patient's social network. Computerized scoring and an interpretive report facilitate use.
- *The SF-36 Health Survey* (SF-36) (94) surveys general health status in terms of physical and mental health and functional status. Widely used in research, and as an outcome measure (95), it assesses 8 areas, including limitations in physical functioning and social functioning and roles and activities, pain, mental health, vitality and health perceptions.
- *The Neurobehavioral Functioning Inventory* (NFI) (96). The NFI is a multipurpose inventory designed to measure current cognitive, physical, and emotional functioning in persons with traumatic brain injury or other neurobehavioral disorders. It is comprised of six independent scales reflecting problems frequently experienced by persons with neurobehavioral disorders: depression, somatic, memory/attention, communication, aggression and motor functioning. This well researched instrument includes separate forms for patient and family, demonstrates concurrent validity with neuropsychological test data and objective personality inventory profiles, can assist with treatment planning and allows measurement of change over time.
- *The Sickness Impact Profile* (SIP) (97) is a behaviorally based measure of health status designed to assess both psychosocial and physical dysfunction. It has sound psychometric properties, is used widely with chronic pain patients and can provide relevant information regarding degree of functional limitation in daily activity.
- *The Illness Behavior Questionnaire* (IBQ:(98, 99)) provides useful information about attitudes, perceived reactions of others and psychosocial variables. It delineates 7 factors that include general hypochondriasis, disease conviction, psychological vs. somatic focusing, affective disturbance, affective inhibition, denial, and irritability. In addition, it has value in identifying patients who rely on illness behaviors as a coping style for need procurement.

TABLE 39-3 (continued)

**General Psychological Measures: Mood, Anger and Anxiety**

- *The Beck Depression Inventory – 2 (BDI-2)* (100) is a common self-report measure that assesses depressive symptomatology. It has been reported to differentiate chronic pain patients with and without major depression utilizing an optimal cutoff score of 21 (101) and has well documented predictive validity.
- *The Zung Self-rating Depression Scale (SDS)* (102), seems especially well suited for medical settings, and has several advantages over other measures. It is shorter, simpler to administer and score, requires a lower reading level, fits well with medical and injury situations and can be easily administered in an interview format (62). Items are self ratings on a scale ranging from 1 to 4 (“Not at all” to “Most or all of the time”) and are scored in the direction of increased depressive symptomatology, with a raw score cutoff for mild depression of approximately 40 points.
- *The State-Trait Anger Expression Inventory-2 (STAXI-2)* (103) and its recent update is a reliable, well-normed instrument for assessing the experience, expression and control of both current state and trait anger. Anger Expression and Anger Control scales assess four relatively independent anger-related traits: (a) expression of anger outward; (b) holding anger in; (c) controlling outward expression; and (d) controlling internal angry feelings. This instrument provides information regarding how experience, expression and control of anger may contribute to psychophysiologic arousal and symptoms and increase risk for developing somatic symptoms and medical problems. Indirectly, it offers suggestions for the direction of appropriate interventions. Importantly, anger is a frequent concomitant of chronic pain that has been unfortunately underappreciated (57).
- *The Beck Anxiety Inventory (BAI)* (104) is a screening measure of severity of patient anxiety. Specifically designed to reduce overlap with symptoms of depression, it assesses both physiological and cognitive components of anxiety in 21 items describing subjective, somatic, or panic-related symptoms. The BAI differentiates well between anxious and non-anxious groups in a variety of clinical settings.
- *The Perceived Stress Scale (PSS)* (105) is a widely used instrument for measuring the degree to which situations in one’s life are appraised as stressful. Items measure how unpredictable, uncontrollable, and overloaded respondents find their lives and directly queries current levels of experienced stress. Higher PSS scores have been associated with greater vulnerability physical and psychological symptoms following stressful life events.

**Comprehensive Personality Assessment Instruments**

- *The Minnesota Multiphasic Personality Inventory (MMPI)*:(106) *MMPI-2* (107) ) is the most widely used psychological assessment instrument in the US. The MMPI is a 567 item (true/false) objective measure of personality function and emotional status with 10 clinical and 3 (7 in revised version) validity scales that were derived through empirical discrimination). Its predictive abilities are based on more than fifty years of actuarial data collection and analysis. It is a very sensitive measure of psychological states, traits and styles (e.g., excessive anxiety, tension, depression, hostility and problematic anger, somatization tendencies, sociopathy, substance abuse, deviant thinking and experience, social withdrawal, etc.). Through configural interpretation of the relative scale elevations, tentative hypothesis regarding personality and coping style and relative degree of particular types of psychological disturbance can be gleaned. Importantly, although the MMPI can and is frequently misused and misinterpreted (e.g., application of psychiatric norms to medical patients tends to beg psychiatric interpretations), it represents one of the most useful adjuncts to personality assessment and treatment planning. A cursory summary of potential utility of MMPI profile interpretation for assessing psychological reactions and contributions to physical conditions was offered by Fordyce (101), and roughly includes configural guidelines for interpreting: 1) Willingness to display physical symptom behaviors; 2) Distress/discomfort about illness (“How comfortably sick?”); 3) Poor general coping skills; 4) Depression complicating physical symptoms; 5) Tension (and sympathetic arousal) contributing to physical symptoms (High back, head, neck, shoulder, etc.); 6) Treatment outcome issues. A number of subtypes of chronic have been identified by other researchers although, as with other measures, it remains unclear to what extent results may inform the degree to which complaints are associated with organic (especially peripheral pathology) versus psychologic contributions to patient presentation (108, 109).
- *The Personality Assessment Inventory (PAI)* (110) a good measure of general psychopathology that can help with identification of a wide variety of risk factors that could adversely affect adjustment. It has good psychometric properties and contains 340 items, with 22 scales, including 4 validity scales. As with most other general psychological assessment measures, it has no norms for chronic pain and tends to overpathologize this group.
- *Millon Clinical Multiaxial Inventory, 3rd edition (MCMI-III)*: (111): includes scales assessing DSM-IV based psychiatric disorders, including affective, personality and psychotic disorders, somatization and others. It is useful for the differential diagnosis of personality disorders and psychological vulnerabilities for adaptation to pain. Like other psychiatric measures, it has limited pain group norms and may be prone to overpathologizing patients.

TABLE 39-3 (continued)

**Pain Assessment Measures with Built In Response Bias Indicators**

Pain Assessment Battery (PAB) (89): – Research Edition:  
Proposed clinical hypothesis procedure evaluating:

- Symptom Magnification Frequency (SMF) > 40%
- Extreme Beliefs Frequency (EBF) > 35%
- Four other “validity” indicators (i.e., alienation, rating percent of max, % extreme ratings (2 scales)

Millon Behavioral Health Inventory (MBHI) (93)

Elevation on three built-in validity scales

Hendler Chronic Pain Screening Test (87)

- Scores of 21–31 (Exaggerating)
- Scores >31 (Primary psychological influence)

**Factors Suggestive of Significant Exaggeration, Illness Behavior or Malingering**

Main & Spanswick Indicators (112)

- Failure to comply with reasonable treatment
- Report of severe pain with no associated psychological effects
- Marked inconsistencies in effects of pain on general activities
- Poor work record and history of persistent appeals against awards
- Previous litigation

These instruments are intended to be integrated with a thorough history taking, interview of patient and relevant others as available, and examination of relevant medical and allied health records.

The understanding derived from a comprehensive biopsychosocial pain assessment provides the framework for designing individually tailored treatment interventions and recommendations. Examining the impact of various cognitive processes on the subjective perception of the patient's pain is a critical component of this comprehensive assessment. Turk (113) has emphasized the importance of understanding and addressing the important role of patient pain appraisals, beliefs and expectancies. He, and others (e.g., Asmundson, Nicholas & Carleton (114)), note that patients with chronic pain resulting from traumatic events are predisposed to experiencing physical sensations as harmful and noxious which increases both anxiety and subjective pain perceptions. This, in turn, leads to further activity avoidance and functional limitations that block recovery and facilitate increased deconditioning, creating increased risk for developing chronic and disabling pain.

Important psychoemotional components relevant to the assessment of chronic pain (115) include: the subjective experience of pain; autonomic arousal associated with bodily reactions to pain; cognitive appraisal(s) of the painful experience as related to the personal meaning of the pain or the historically learned responses to pain and injury; non-verbal behaviors including facial expressions and body language associated with pain; and affective reactions to pain, including anxiety and depression. Persons with chronic pain have a much higher predilection and incidence of depression and anxiety as well as anger. A diathesis-stress model has been proposed to explain the higher rate of depression in this patient population, and likely applies to other psychoemotional responses to chronic pain (116).

Finally, pain assessment and treatment strategies are best conceptualized in terms of suitability to a multidimensional process that evolves significantly as it persists over time. The stages of pain processing model (117–119) is an illustrative model that distinguishes the sensory, affective, cognitive-evaluative, and behavioral dimensions of pain as it changes with increasing chronicity. The first two stages involve sensory discrimination and associated affective responses. The former is commonly assessed by ratings of pain intensity and location, while the latter is assessed by ratings of pain unpleasantness. The third stage involves the meaning and implications of pain for the patient and associated emotional suffering, and is commonly assessed by measuring pain-related emotional states (e.g., depression, anxiety, frustration) and beliefs (e.g., perceived ability to control or endure pain). The fourth stage refers to illness behavior (e.g., lifestyle and role disruption, avoidance) and can be assessed through self and collaborated ratings and observation (e.g., pain behaviors manifested at home, work, clinical interview). As pain persists, there is a transition of the focus of assessment from the first two stages to the latter two.

**Response Bias Assessment**

Diagnosis and treatment is the usual reason for assessment of chronic pain, along with impairment and disability evaluation in compensation situations. Importantly, assessments can involve contexts with strong financial, personal, social and/or other incentives. Hence, chronic pain patients may present with response bias, or the tendency to report or present pain or related disability in a less than fully truthful, accurate or valid fashion. For example, many assessments occur in such forensic contexts as health care insurance policy coverage, disability insurance policy

application, social security disability application, personal injury litigation, worker's compensation claims, functional capacity evaluations and determination of capacity for work. These contexts often present strong financial (120) and numerous other and often more powerful vocational, social, personal and other incentives (see Martelli, Nicholson et al., Chapter 64, in this text).

Response bias in pain presentation can range from symptom minimization to symptom exaggeration and malingering. Hence, assessment of examinee veracity in report and attribution of symptoms, and motivation during presentation and assessment, becomes critical with regard to increasing diagnostic accuracy. This is prerequisite to provision of appropriate and timely treatment, prevention of iatrogenic impairment and disability reinforcement, and appropriate legal compensation decisions (Martelli, Nicholson, Zasler & Bender, Chapter 64 in this text).

A thorough analysis of response bias in chronic pain is beyond the scope of this chapter. Chapters that more fully explore the topic of response bias assessment in chronic pain can be found in Martelli, Zasler, Nicholson et al. (121) and Nicholson and Martelli (36). Chapter 64 in this text is specifically devoted to the general assessment of response bias and provides background, relevant measures and a general model for assessment. Measures specific to response bias regarding pain report are included, and readers are referred to that chapter for a detailed review. Additional pain response bias measures with potential utility are included in Table 39-3.

Importantly, because Chapter 64 emphasizes assessment of neurocognitive response bias, additional clarification of the unique nature of pain and the challenges in pain assessment is indicated. Pain, unlike cognitive impairment from brain injury, is a subjective complaint that is more viscerally, directly and universally noxious. It is much more difficult to assess than neurocognitive impairment due to limitations of existing measures and is, in fact, extremely difficult to verify or refute. (122–128). Assessment of pain presents a significant diagnostic challenge for all but the most conspicuous cases of severe, functionally disabling physical pathology. The advances that are being made in assessment, treatment and outcomes in chronic pain owe to new biopsychosocial models and psychophysiological advancements. These are based on discarding simple dichotomous models in favor of evidence of central processing factors and psychophysiologic etiologies, as a preponderance of data are accumulating to indicate that chronic pain is often represented in dysfunctional cerebral processing and not only the same peripheral mechanisms as acute pain on which medical assessments are more usually conducted (24, 35).

Unfortunately, there remains predominant overrepresentation of simplistic and uninformed dichotomous pain conceptualizations. These persist despite failed

attempts to make dichotomous discriminations between “organic” and “nonorganic” pain using either medical or psychological measures. For example, in Fishbain et al's (126, 127) metaanalytic review, it was concluded that the Waddell signs, the most relied upon measure of “non-organicity” in medicine and physical therapy, are invalid. That is, even when properly used, they do not discriminate organic from nonorganic problems, are associated with higher pain levels, may represent an organic phenomenon and are neither correlated with psychological distress or secondary gain. It shouldn't be surprising that many psychological measures have proven inadequate, given that they were derived from prediction of physical measures of nonorganicity that were invalid.

The lack of any reliable or valid measures of presence or degree of pain and pain exaggeration or malingering necessarily weakens the utility of psychological measures designed to make such predictions. Nonetheless, attempts to develop methods and guidelines for the detection of response bias and malingered pain are continuing. Malingering, or the act of willful, deliberate, and fraudulent feigning, or significant exaggeration of pain is only one variant of response bias, and an extreme one. The presence of response bias, which may not be an uncommon response to aversive stimuli, is much more easily documented than malingering. However, the two are often confounded and used synonymously in professional neuropsychological publications and practice, where response bias measures are frequently referred to, explicitly or implicitly, as “malingering tests”. Inferences about malingering, especially in a restrictive health care environment with strong gate keeping pressures, are inherently problematic. In the absence of dependent measures or clinical methods with demonstrated validity for assessment of possible malingering of pain, inferences about pain malingering using current measures and procedures necessarily produce fallible judgments with unknown false positive rates.

Despite the absence of reliable or valid measures and methodologies for detecting degree of pain exaggeration or malingering (35, 124, 128–130), estimates, unreliable as they must be, have been proffered. Fishbain (124) in his systematic review of available samples and methodologies estimated that malingering may occur in 1.25 – 10.4% of chronic pain patients, while Mendelson and Mendelson (129) concluded that notable exaggeration or malingering of chronic pain across settings is less than 20%.

However, it must be emphasized that, in the case of chronic pain, malingering and exaggeration are usually distinct entities that are not simply differentiated by degree. Exaggeration, which appears much more commonly, can be distinguished from malingering in several important ways. While deliberate exaggeration and malingering are typically driven by external monetary or other incentives, chronic pain mechanisms frequently

involve dysregulation of central pain processing mechanisms and derive from exaggerated neurophysiologic pain responses (see Zasler, et al., Chapter 41 in this text), including allodynia (pain from stimuli that are not usually painful), hyperalgesia (increased response to painful stimuli) and hyperesthesia (abnormal acuteness of sensitivity to sensory stimuli). In addition, suboptimal psychological adaptation to chronic pain frequently involves catastrophization and related processes rather than exaggeration for purposes of monetary or other secondary gain. Finally, pain is, by nature, highly aversive and associated with physiologic and behavioral avoidance reflexes that are genetically programmed and present at birth, and accompanied by anxieties and aversive emotions that are both highly conditionable and strongly and inherently disruptive of adaptive behavior. This not only makes differentiating exaggerated from non-exaggerated pain responses difficult and necessarily reliant on value judgments, but represents a clearly distinct phenomenon in contrast with exaggeration for the purposes of secondary gain.

The task of making determinations regarding genuine pain severity and impact and related functional impairment and disability is complicated by numerous factors. These factors are not necessarily fully appreciated except by the most informed chronic pain management specialists, and usually misunderstood by nonspecialists. These factors should be considered as reasons for considerable caution in making inferences about response bias and malingering during chronic pain assessments. In brief summary, they include:

- The subjective and complex nature of pain, as previously noted;
  - The lack of valid measures of presence, severity, exaggeration or malingering of pain;
  - The lack of formal, scientifically validated conceptual models and “rating systems” of pain associated impairment and disability;
  - Numerous methodological problems with response bias assessment measures generally, including those designed for domains that are much easier to assess than chronic pain (e.g., problems with reliability, validity; sensitivity, specificity, misclassification, generalizability, lack of mutual exclusion, etc.; see Chapter 64 in this text for a review of generally problems with available response bias measures)
  - The challenge of disentangling not only the multiple contributors to subjective pain experience, but also to associated functional disability;
  - The context of assessment, where referral may be for treatment or compensation (e.g., where the latter is typically associated with higher rates of response bias and malingering; see Chapter 64 in this text) and numerous factors may be exerting motivational influence
- The nature of aversive events and anxiety, which are known to produce strong classical and operant conditioning, especially relating to avoidance behavior, and to decompensate efficient behavior and adaptation in animals and humans. That is, pain, by its aversive nature, predisposes organisms to avoidance as a typically adaptive, biological survival mechanism. However, the presence of anxiety, distress and avoidance behavior is often misinterpreted as a sign of “nonorganicity”, exaggeration and/or malingering in physical examinations, or as a psychogenic etiologic factor, when evidence indicates it is most often a reaction to pain or an indicator of severity (14, 59, 126, 127). The failure of the highly relied upon Waddell signs as a purported indicator of nonorganicity, and the evidence that they are in fact not associated with secondary gain and appear more associated with organic phenomenon and severity of pain, is a good illustration of how this misconception has contributed to misdiagnosis and associated misunderstanding and mistreatment of persons with chronic pain.
  - Western cultural tendencies to interpret distress responses and avoidance to aversive pain experience as inherently pathological. Evidence of this comes from the misrepresentation and misinterpretation of the “fight-flight” response. The overwhelming majority of ethological and human evidence indicates that flight attempts almost invariably precede fight attempts in coping with aversive events, in the following sequence: freeze, flee, fight, fright (131). In fact, adaptation to chronic pain requires learning to overcome the avoidance responses that are innate to all organisms.
  - The distinct nature of exaggeration versus malingering of pain. Mechanisms underlying development of central and peripheral sensitization that lead to allodynia and hyperesthesia are becoming better understood. These, by definition and appearance, represent an exaggerated response. However, they are neurophysiologically based and not driven by external incentives like secondary gain. Similarly, pain catastrophization and related processes represents an exaggerated pain response, but are explained by suboptimal psychological coping and must be differentiated from deliberate exaggeration for purposes of secondary gain.
  - The critically important distinction between acute and chronic pain. Chronic pain is distinct from acute pain not only with regard to the absence of clearly identifiable peripheral tissue damage or neuroanatomical pathways, but, as recent neuroscience evidence shows, also in terms of how it is processed in the central nervous system. In addition to previously noted differences, recent reviews of functional

neuroimaging studies clearly demonstrate that chronic pain is processed differently than acute pain both in terms of the lateral versus medial pain systems and the activation of affective-evaluative mechanisms (see Zasler, et al, chapter 39 in this text, or Apakarian (6) for a review). When these distinctions are blurred, and chronic pain is assessed in terms of standards for acute pain, as is generally practiced in medicine and psychology, the absence of clearly identifiable pain triggers and greater emotional activation leads to conclusions that erroneously infer deliberate exaggeration and malingering. Given strong external incentives in a restrictive health care environment (Martelli et al, in Chapter 64 of this text) with increasing preponderance of insurance and adversarial medicolegal referrals, an inflation of false positive diagnoses of malingering might be expected.

The unique nature of chronic pain and limitations with regard to its assessment require caution with regard to over-interpretation of response bias procedures and emphasize the importance of integrating multiple data sources and making thoughtful inferences only after integration of thorough historical information, interview, assessment, behavioral observations, collaborative interview and data sources, and so on. Importantly, Martelli (132) and Nicholson (133) have argued that assessments conducted by persons without specialty chronic pain training and experience likely violate professional ethical standards.

## PAIN MANAGEMENT

Early after the emergence of pain, and when pain is in the acute stage, treatment interventions invariably address amelioration of distress, correction of underlying pathophysiology and promotion of healing. Inherent in all pain management interventions is the prevention of chronicity, which is undoubtedly the most important purpose and most effective accomplishment in pain management. Zasler et al. (Chapter 39 in this text) address the medical approaches involving assessment and treatment of acute pain. They emphasize the importance of effective assessment and treatment by using the compliment of medical and pharmacologic agents and other strategies designed to minimize distress while correcting underlying pathophysiology and restoring function. Although acute pain management interventions are primarily medical in nature, behavioral and psychological pain management interventions still play an important role in cases where associated psychological distress is significant, medical interventions do not produce expected pain relief, and/or where correction of pathology is complicated or where

traditional analgesic medications or other medical interventions cannot be employed.

Unfortunately, acute pain is not always resolved. As it persists, it becomes chronic and more intractable. The goal of preventing chronicity gradually transforms to include reducing the severity and persistence of pain related distress, associated psychological and physical symptoms, functional disability and life interference, and improving adaptation and coping with pain. Although the goals of comprehensive chronic pain management interventions can vary with individuals and settings, they can generally be summarized as addressing the following areas:

- Modulation and reduction of intensity, frequency and duration of sensory, as well as cognitive-evaluative and affective distress responses related to pain experience
- Modulation and reduction of associated physical and psychological symptoms and concomitants of pain, especially as they relate to mood and emotions, cognition, energy, sleep, eating, physiological arousal and general physical and emotional health
- Reduction of functional disability, maladaptive avoidance and illness behavior, and interference with regular and preferred activities, including regular daily activities and preferred family, social, avocational, vocational and recreational function and activities
- Increasing self management to actively utilize available strategies to minimize pain related distress, functional disability and life interference

Because persistent pain may be associated with a combination of physical and psychological factors, combination treatments and a multidisciplinary approach to chronic pain management, consisting of pain specialists in medicine, psychology, physical therapy, occupational and/or vocational and/or other allied health professions, are indicated. This approach is widely accepted as the most clinically successful and cost effective process in treating chronic pain (25, 134–137). This is best conducted, and can usually only be effectively accomplished, within the context of a specialty pain clinic. Specialty pain clinics are the treatment of choice for chronic pain conditions, with clinical efficacy supported by several recent reviews (134, 138–141). Referral to pain management specialists and specialty pain clinics should be considered the standard of care for the treatment of persons with chronic pain.

When the person with pain has also sustained a TBI, additional recommendations are warranted. In persons with TBI and pain, there is evidence that pain is harder to manage (29), that it takes longer to complete a pain management program (142), and that special attention is required because of cognitive difficulties (26).



Hence, referral to pain specialty pain programs with experience in treating persons with TBI, and/or consultation with such providers to allow expectation of extended treatment periods and incorporation of cognitive compensatory strategies, is indicated

### **Model for Conceptualizing Chronic Pain Treatments**

There is considerable evidence and growing acceptance that many or most forms of chronic pain involve central and/or peripheral sensitization (143). Evidence for a neuromuscular conceptualization of many chronic pain problems has grown very fast and represents a convergence of findings across multiple specialties (38). Most forms of chronic pain are now considered (4, 5, 26, 38, 144) to possibly include a hyper-responsiveness of the pain system involving “wind up” or sensitization in the CNS / brain. Conceptually, the thrust of current efforts in chronic pain management seem to be toward “desensitization” of the CNS through combination treatments. In addition, multidisciplinary and multicomponent or combination treatment packages represent the most effective treatments in chronic pain, especially when comorbid with brain injury (3, 20, 31).

The authors have proposed a preliminary classification model for planning and conceptualizing chronic pain management interventions (143, 31). This model, summarized in Table 39-4, can include combination of any of the included treatments. It facilitates the classification of currently available and potentially useful chronic pain treatment approaches according to specific area and manner of desensitization targeted, which can include any of the treatments included. This model offers

a potentially useful classification system for conceptually organizing the wide variety of available treatment interventions and in planning combination treatments.

It should be noted that Tyrer and Lievesley (145), among others, recommend the development of pain management facilities specifically designed for persons with brain injuries. The emotional disturbances associated with pain are also frequently comorbid with TBI, highlighting the importance of a biopsychosocial perspective. Such a perspective allows for a holistic conceptualization of the patient, incorporating multimethod, multimodal assessments that facilitate individualized treatment planning. Treatment goals include not only the reduction/relief from pain, but also increased self-control, increased adaptation to life changes secondary to pain and brain injury, and improved functioning and quality of life.

### **Behavioral–Psychological Management**

Behavioral and psychological services are an important component of comprehensive pain management services. A review by McCracken and Turk (146) identified more than 200 studies confirming that behavioral medicine interventions such as cognitive-behavioral therapy, biofeedback, and relaxation, are effective in reducing pain and pain related distress. Table 39-5 includes a summary of some of the most frequently used and empirically supported strategies. This table borrows from the review by Martelli et al. (3), but readers are referred to additional reading for more comprehensive summaries in the work of McQuay and Moore (147), reviews of evidence-based recommendations for management of chronic non-malignant pain (e.g., College of Physicians and Surgeons (148)), or the

**TABLE 39-4**

*A Desensitization Model for Chronic Pain Treatment Interventions*

**Desensitizing Peripheral CNS Procedures**

- EMG and Temperature Biofeedback; Various Relaxation and Imagery Procedures; Transcutaneous Electrical Nerve Stimulation (TENS)

**Desensitizing CNS Medications**

- Anti-epileptic drugs, tizanidine HCL, Amytal, neuroimmunomodulators, SSRI's etc.

**Desensitizing Behavioral Activity Procedures**

- Operant behavioral activity programs; graduated exposure / graduated activity programs; relaxation, imagery, refocusing; cognitive behavioral reinterpretive strategies

**Desensitizing Psychotherapeutic Procedures**

- Emotional desensitization of catastrophic reaction to injury and pain and other fears and trauma; splinting of emotional reactions and calming of catastrophic reactions and hypervigilance to pain; specific formal pain and fear desensitization procedures; pain exposure / desensitization procedures; cognitive behavioral reinterpretive strategies

**Desensitizing Neurophysiologic Procedures**

- Cranioelectrotherapy Stimulation (CES). Consider EEG Biofeedback or other potentially helpful adjunctive relaxation procedures such as sound and light (AudioVisualStimulation, AVS) and Transcranial Magnetic Stimulation and Brain Electrical Stimulation.

**TABLE 39-5**  
**Summary of Useful Behavioral Treatments for Chronic Pain**

*Patient Education:* The most conspicuous and malleable factor that contributes to psychophysiological arousal and stress responding is patient expectancy and knowledge about symptom management. For example, Ham and Packard (154) found that headache patients that desired an explanation of their headache at least as much as pain relief. In the case of mild TBI, education about expected symptoms and course has been shown to reduce the anxiety and selective attention and misattribution that can unnecessarily prolong symptoms (155). The best education treatment packages generally contain elements targeting numerous factors. Accurate information and expectancies help with this and also assist with coping with pain more adaptively. Stress management information and strategies can assist with reducing sympathetic arousal / discharge that exacerbates pain, while specific postural training and sleep hygiene can assist with postural rehabilitation and normalizing sleep patterns.

*Cognitive-Behavioral Treatments:* Cognitive approaches incorporate the physical, psychological and behavioral aspects of the pain experience in promoting patient self management of pain. They typically emphasize learning of self regulation and self control skills and taking greater personal responsibility for lifestyle habit change, especially with regard to identifying and replacing maladaptive beliefs about pain. Specific training is provided in cognitive strategies and skills to replace such inappropriate negative expectations and beliefs as catastrophization and associated magnification, rumination and helplessness that maintain physiologic arousal and maladaptive avoidance and illness behaviors that complicate symptom resolution (113). A comprehensive multimodal approach should include education, skills acquisition, cognitive and behavioral rehearsal, homework and generalization and maintenance (156).

*Relaxation Training:* Progressive muscle relaxation (PMR) is the most studied relaxation procedure (157). PMR involves the systematic tensing and relaxing of various muscle groups to elicit a deepening relaxation response, usually with combination of muscle groups and addition of diaphragmatic breathing to shorten the protocol. Meta-analytic reviews generally conclude that relaxation training and biofeedback training are equally effective. Relaxation training presumably serves to (1) reduce proprioceptive input to the hypothalamus, thereby decreasing sympathetic nervous system activity (150) and (2) directly reduce muscle tension or pre-headache vasoconstriction (158).

*Operant Treatment:* Operant based treatment strategies require altering environmental contingencies to eliminate reinforcement of pain and illness behaviors (e.g., verbal complaints, inactivity, avoidance) while rewarding "well" behaviors (e.g., incrementally increased exercise, activity level, involvement and participation).

*Biofeedback:* Extensive research supports the utility of EMG or thermal biofeedback for headache pain, and chronic musculoskeletal pain disorders more generally. The forehead, trapezii, frontal-posterior neck, and neck areas are frequent EMG feedback sites. Patterns of pathophysiologic neuromuscular activity that underlie pain complaint and functional limitations, which can be remediated through feeding back physiologic information to allow self-correction, include: a) Stress-related hyperarousal in musculoskeletal or other physiologic systems; b) Postural dysfunction; c) Hyper- or hypotonicity induced by reflex systems activated by inflammation, active trigger points and cumulative strain or recurrent trauma; d) Learned guarding or bracing to mitigate anticipated pain or injury; e) Learned inhibition or avoidance of muscle activation / activity; f) Chronic compensation for joint hypermobility/hypomobility (e.g., muscles taking over the role of damaged joint tissue); f) Faulty motor schema and muscle imbalance reflecting development of one or more of the preceding syndromes, and resulting in the lack of coordination and stability between typically coordinated muscle groups. Recently, data are emerging which indicates that EEG biofeedback, and associated EEG driven stimulation offers efficacy in treatment of some persistent pain and persistent post-concussive symptoms (159, 160). Finally, evidence has been reported that individuals can gain specific voluntary control over rostral anterior cingulate activation to directly control pain perception in severe, chronic clinical pain (161).

*Social and Assertiveness Skills Training:* Skills training may help some patients with more effective communication of needs. Increased need fulfillment decreases distressful emotions which reduces physiological arousal that contributes to pain experience (162).

*Imagery and Hypnosis:* Using some combination of autohypnosis, suggestions of relaxation and visual imagery, patients are generally instructed to visualize the pain (i.e., give it form) and focus on altering the image to reduce the pain. Imagery based treatment is most effective following establishment of a good therapeutic alliance in order to facilitate compliance (163).

*Habit Reversal:* These treatment packages teach pain patients to detect, interrupt, and reverse maladaptive habits (e.g., maladaptive head/jaw posture, jaw tension, negative cognitions). Specific skills are taught to both reverse poor functional habits and stressful thoughts as well as feelings that precipitate/perpetuate them (164).

many systematic reviews prepared for the Cochrane Collaboration (149). Although there is a paucity of studies examining pain management in persons with TBI, the interventions used are the same, qualified by understanding that treatment may take somewhat longer and require cognitive compensatory strategies, commensurate with cognitive impairments, to assist with learning.

When persons with TBI initially present to psychologists for pain management services, the initial assessment process is always benefited by establishment of a therapeutic rapport. This includes countering any patient resistances or misconceptions (e.g., that pain must be in “their head” because they are seeing a psychologist) and engendering accurately informed and hopeful expectancies. Psychological management of persons with pain and TBI begins with an assessment that identifies all variables relevant for treatment. In addition to areas such as personality and emotional status, coping style and strategies, social support, and pain specific factors (see Table 39-3 and preceding pain assessment section), evaluation must also include specific sequelae associated with brain injury. An integration of this information is necessary to ensure that the full constellation of residual sequelae and strengths are considered to optimize an individually designed treatment plan that anticipates and implements compensatory strategies for all potential obstacles to benefit from behavioral interventions. For example, deficits in memory, attention, or executive functioning might be addressed through task-analytic instruction and compensatory memory notebooks with provision of external reminders for completion of at-home assignments. The patients specifically tailored treatment plan should provide a framework and outline for treatment, define goals and patient / therapist expectations and sequences, and provide psychoeducational information about the particular type of chronic pain and rationale for treatment.

Despite the previously noted dearth of outcome studies examining the behavioral treatment of pain after traumatic brain injury, the available literature suggests general similarities in clinical presentations, pathophysiologies and treatment responses, with somewhat greater similarities for traumatic versus not traumatic chronic pain, and some evidence suggesting greater treatment resistance for the latter type (150).

In cases of post traumatic pain, the severity and frequency of pain attacks or exacerbations and chronic pain-related sequelae such as coping abilities, depression, and anxiety are significantly improved by combined psychological treatment protocols (64, 151–153). Supportive counseling that begins early after trauma and is continuous results in better patient response (64).

Table 39-5 includes a summary of some of the most frequently used and empirically supported strategies (3), but readers are again referred to additional reading for more comprehensive summaries (McQuay & Moore (147);

College of Physicians and Surgeons (148); The Cochrane Library (149)).

## Conclusion

Chronic pain is a frequent concomitant of TBI. However, the assessment and treatment of persons with pain is a complicated and challenging process. Pain, by itself, can have a more disabling effect across a wider range of functions than brain or many other types of injuries. In addition to the absence of clear and objective measures for assessment and monitoring of pain, pervasive misconceptions dominate modern medical and psychological practice. Fortunately, recent advances in chronic pain assessment and treatment can be attributed to adoption of a biopsychosocial perspective. The most promising current treatment interventions are combination treatments that are holistic in nature and target the patient’s reaction to pain within his/her daily life and ability to exercise self-control. Multicomponent treatment packages are currently the preferred treatment choice for chronic pain (3, 20, 162), especially when it accompanies TBI. The current chapter is intended to promote familiarity with many important issues and current knowledge required to increase awareness and understanding of psychological approaches to assessment and management of pain in persons with TBI. This will hopefully assist with the making of appropriate referrals, and promoting effective carryover and integration of pain management principles into care of persons with concomitant TBI.

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# 40

## Neurorehabilitation Nursing of Persons with TBI: From Injury to Recovery

*Terri Antoinette*

### INTRODUCTION

It is critical for nurses who will provide neurorehabilitation nursing care to persons who have sustained a traumatic brain injury (TBI) to possess highly specialized knowledge and acute clinical assessment skills. This must be based on an understanding of the pathophysiologic effects of the TBI, the potential medical complications which can affect all body systems, and the physical, cognitive, neurobehavioral, psychosocial, and functional impact of the TBI on the person and the significant others in his/her life.

The delivery of rehabilitation nursing care extends far beyond the delivery of care at the bedside. The licensed, registered, professional nurse: (1) collaboratively practices with the physician and the interdisciplinary team to implement rehabilitation interventions based on evidenced-based practice, (2) provides ongoing support and supervision to licensed practical nurses and direct care givers (i.e. certified nursing assistants) in the delivery of quality care, and (3) conducts patient/family teaching to promote the achievement of individualized quality outcomes.

This chapter presents an overview of neurorehabilitation nursing care issues throughout the continuum of care from prehospital management through acute/ sub-acute, neurobehavioral, and post-acute rehabilitation.

### PRIMARY AND SECONDARY BRAIN INJURY

Primary brain injuries occur at the time of impact and result from an immediate biomechanical disruption of brain tissue and vasculature. Primary injuries may include: (1) concussions, contusions, lacerations, and skull fractures, (2) epidural, subdural and intracerebral hematomas, (3) penetrating injuries, (4) subarachnoid and intraventricular, hemorrhages, and (5) diffuse axonal injuries (DAI) (1, 2).

Secondary brain injuries may begin within minutes after the initial injury and throughout the early post-traumatic hours, days, and weeks. The pathophysiology of secondary injury has numerous etiologies. This include neurochemical changes and physiological events which precipitate a metabolic cascade effect followed by cerebral edema, increased intracranial pressure (ICP) and increased metabolic demand with resultant hypoxia, cerebral ischemia, impaired cerebral autoregulation, altered ion homeostasis, additional neuronal destruction, and cell death (2-7).

In a study by Jones et al. (8), involving 124 severely injured patients, 91% were found to have secondary injuries and mortality was associated with the duration of hypotension, hypoxia, and hyperthermia (9). The role of the nurse is paramount in the assessment, intervention and ultimate prevention and minimization of these injuries.



## PREHOSPITAL NURSING CARE

The Guidelines for the Management of Severe Head Injury (10–12) provide evidence-based recommendations for practice which guide the delivery of critical care nursing interventions and clinical pathways from pre-hospital resuscitation through intensive care treatment to adults who have sustained a severe TBI with Glasgow Coma Scores (GCS) of 3 to 8 (13–18).

Critical care nurses may be involved in the care of the patient both at the scene as well as in route to the emergency department. Prompt intervention at the scene has been associated with improved outcome. An advanced trauma life support (ATLS) evaluation is conducted and the person's airway, breathing and circulation assessed. Fluid resuscitation is initiated with isotonic solutions, a patent airway established, ventilation and rapid physiologic resuscitation performed and emergency intervention for multisystem injuries instituted (10–12, 16–18).

Although the incidence of concomitant cervical spinal cord injuries has been cited as 2%–6% (19–21), iatrogenic post-traumatic spinal cord injuries after arrival to the hospital have been estimated to range from 10% to 25% (22). Emergency nursing and paramedic personnel should implement spinal cord injury precautions specific to modification of resuscitative techniques, airway stabilization, neck immobilization and spinal stabilization (16, 19).

During the brief pre-hospital assessment phase, the nurse should continuously assess vital signs (pulse, respiration, blood pressure and pain), perform the Glasgow Coma Scale, and observe pupillary responses for size, shape, symmetry and reactivity to light, eye position, and extraocular movement. Observation should also occur for fluid/bleeding from the ears or nares and a determination made as to whether or not the fluid is cerebral spinal fluid (CSF). Additional assessments to be performed include muscle strength grading and observation for weakness, asymmetry of facial movements, paralysis, pain, decerebrate and decorticate posturing (4, 5, 17, 18, 23).

The skill of the nurse in astutely assessing the patient is of paramount importance. These assessment findings serve as a baseline of comparison for subsequent serial neurological exams, for interventional decision making, and for evaluating treatment effectiveness to minimize secondary brain injury (6, 15).

Valuable information to obtain from the patient, or if not possible, from witnesses at the scene include: (1) mechanism of injury (e.g. blow to the head, fall, ejection from the vehicle), (2) time of injury and extrication time, (3) presence of protective devices (e.g. seat belt, airbags, helmet), (4) loss of consciousness or change in cognitive status, (5) progressively worsening headache, repeated vomiting, (6) periods of apnea or cyanosis, (7) the presence of hypotension (8), amount of blood loss, (9) signs

of substance abuse, (10) the position in which the person was found (i.e. lying face down) and (11) medication history (5, 16, 19, 23).

If the person is conscious and able to converse, a history should be taken and an assessment of level of consciousness (LOC) should include orientation to person, time, place, and situation, assessment of confusion, attention, level of arousal and the ability to follow commands (5, 16, 23).

Key determinants of survival are the adequacy of resuscitation efforts (restoration of circulating blood volume, blood pressure, oxygenation and ventilation), the identification of injury severity and the expeditious transfer to a facility with neurosurgical capabilities (10–12, 15).

## CRITICAL CARE NURSING MANAGEMENT

This section will focus on the rationale and the general principles which guide the nursing care of the TBI patient in the ICU. The reader is referred to other chapters in this text for more detailed, clinically specific information regarding acute management.

The priority of nursing care in the ICU is protecting the brain from secondary injury and includes: (1) maintaining the ICP and cerebral perfusion pressure (CPP) within normal limits, (2) avoiding systemic hypotension, hypoxia, and hypercapnia, (3) controlling cerebral metabolic rate (e.g. seizure control, normothermia, sedation) (4) assuring adequate fluid volume status, (5) maintaining serum glucose level at 80–120mg/dL, and (6) providing nutritional support. The use of mannitol, barbiturates and hyperventilation will vary depending on the course and severity of neurological deterioration (3, 6, 10–12, 18).

Because of the extreme sensitivity of the traumatized brain, the nurse must conscientiously interpret the benefits and risks of each potential intervention. Implementing clinically appropriate treatment is paramount because even a brief delay can result in further neurological insult (3).

### Hypoxia

Immediate correction is imperative for episodes of hypoxia (partial pressure of arterial oxygen (PaO<sub>2</sub>) less than 60mmHg or arterial oxygen saturation (SaO<sub>2</sub>) less than 90% if pulse oximetry is used). Studies from the Traumatic Coma Data bank reported a mortality rate of 50% for patients with hypoxia versus 27% for those without (8, 18, 24).

Acute respiratory failure has been reported in 20% of patients with neurological trauma (6, 25). Ongoing assessment of respirations includes airway clearance, rate,

pattern and characteristics of breath sounds, and monitoring of arterial blood gas (ABG), and oxygen saturation levels. In ventilated patients, the nurse must detect airway obstruction complications by monitoring the position of tubes, cuff pressures and problems with mucous plugs. An ambu bag and mask must be available for emergency use (26).

Early detection of respiratory complications is paramount. A study from the Traumatic Coma Data Bank revealed that 41% of patients in the study developed pneumonia and pulmonary insufficiency was reported in 28% (8, 27). Other complications include adult respiratory distress syndrome, pulmonary contusion, neurogenic pulmonary edema, pulmonary empyema, atelectasis, pulmonary embolus, hemothorax or pneumothorax (6, 18).

### **Hypotension**

The nurse must immediately intervene to correct hypotension (systolic blood pressure less than 90 mm Hg). Hypotension that is tolerated in healthy individuals is not well tolerated in the injured brain and can lead to disruption of cerebrovascular autoregulation, a drop in CPP, elevated ICP and ischemic injury (3, 8).

Chestnut et al. (24) reported that a single episode of hypotension from the time of injury through resuscitation increased mortality 150% and also increased morbidity. Fearnside, (28) in a prospective study, reported that hypotension occurring anytime during a patient's pre-hospital and in-hospital course independently predicted increased mortality and morbidity.

### **Increased ICP**

Increased ICP significantly influences morbidity and mortality. Saul et al. (29) reported a mortality rate of 15% for patients whose ICP remained below 25 mm Hg as opposed to 69% for those persons with ICP values in excess of 25 mm Hg. ICP values greater than 40 mm Hg is considered to be intracranial hypertension that is life threatening (8, 29, 30).

Cushing's triad (hypertension/widening pulse pressure, bradycardia and irregular respiratory pattern) is an ominous sign associated with rising ICP, pressure on the medullary center of the brainstem and irreversible damage (6, 16).

### **Suctioning**

Since ICP can increase with endotracheal suctioning, it is important that the nurse adhere to patient specific protocols regarding the timing and appropriateness of the procedure, administration of medication prior to the procedure, hyperoxygenation of the lungs before suctioning, and instructions specific to the number and time limits for

each of the suctioning attempts. Suctioning of the nasal passage should not occur until the possibility of basal skull fracture and dural tear have been ruled out (6, 14, 26).

### **Positioning**

One of the most frequently performed activities that ICU nurses perform is that of therapeutically positioning the patient. Prior to any positioning it is imperative that spinal cord injury is ruled out. It is important to maintain neutral alignment of the head and neck and avoid disruption of cerebral venous outflow due to tight cervical collars or taped endotracheal tubes. Rotation of the head and flexion of the neck can increase ICP, decrease jugular venous outflow, and affect changes in cerebral blood flow (3, 14, 31–34).

Positioning recommendations based on neurological criteria, while at times conflicting, generally cite that elevating the head of the bed up to 30 degrees may decrease ICP, enhance venous return and decrease cerebral vasoconstriction. Caution must be taken, however, because cardiovascular, pulmonary and other body system responses to positioning may influence hemodynamic stability, cerebral perfusion pressure and systemic oxygenation. For example, in patients who are hypovolemic, hypotension may worsen if the head of the bed is elevated (3, 14, 31–35).

Turning and repositioning for contracture and spasticity management and to prevent skin breakdown must also be considered. Hip flexion of greater than 90 degrees may also elevate ICP. It is important for the nurse to obtain individualized patient specific instructions from the physician regarding positioning (3, 14, 18, 31–34, 36).

### **Nutrition**

The body's initial response to severe TBI is that of a hypermetabolic/ hypercatabolic state. The Guidelines for the Management of Severe Head Injury recommend enteral or parenteral nutrition (particularly jejunal feeding) to replace 140% of resting metabolism expenditure in nonparalyzed patients and 100% in paralyzed patients (10–12, 16).

Options for feeding include parenteral, enteral-gastric and enteral-jejunal. Advantages of jejunal feeding include: (1) improved absorption of nutrients and gastric tolerance, (2) improved nitrogen retention (3) greater increases in serum prealbumin, (4) increased caloric intake, and (5) lower rate of pneumonia. When compared with parenteral feeding, the advantage of jejunal feeding includes: (1) lower theoretical risk of infection and sepsis, (2) decreased risk of hyperglycemia, and (3) lower cost. Once gastric tolerance is attained, enteral gastric feedings have practical advantages specific to the resumption of the normal digestive process and the capability for the delivery of bolus feedings (10–12, 18, 37–39).

### **Neurological Complications**

In order to recognize subtle neurological improvement or deterioration, nurses must perform a systematic, organized neurological assessment which includes the Glasgow Coma Scale, level of consciousness (arousal, awareness, higher cognitive functioning, speech and language), pupillary reflexes, cranial nerve function, sensory and motor function, and deep tendon reflexes. A Mini-Mental Status Examination should be done when clinically appropriate (4, 40).

The nurse should be able to accurately describe and recognize all classifications of seizures. Familiarity with the patient's history in regard to the time and onset of seizures, side effects of anticonvulsants, and familiarity with the recommendations for anticonvulsants from the Severe Head Injury Guidelines is paramount (10–12). Detailed information regarding neurological complications will be discussed elsewhere in this text.

### **Pain**

Pain can adversely effect ICP and CPP and interfere with the accuracy of some parameters of vital signs and neurological assessment (e.g. pupillary response, sedation). If the patient is unable to consciously respond to questions regarding pain intensity, it is important for the nurse to observe for facial grimacing, body movement, crying, restlessness, elevated blood pressure and heart rate and agitation (6).

### **Multisystem Complications**

Stabilization of systemic injuries is paramount to minimize blood loss and to prevent complications. The patient is also at risk for the development of multisystem complications such as coagulation disorders, deep venous thrombosis (DVT), cardiac arrhythmias, syndrome of inappropriate anti-diuretic hormone, electrolyte abnormalities, and glucose fluctuations. Nosocomial infections (i.e. pulmonary, urinary tract, vascular catheter, and wound) can be life threatening and require prompt assessment and appropriate treatment. Serious gastric complications include the development of stress ulcers, gastrointestinal bleeding, malabsorption syndromes and increased potential of aspiration. Hyperthermia must be closely monitored and rapidly treated (antipyretics, cooling blankets and antibiotics when indicated) since it increases cerebral metabolic demands (4, 5, 18, 41).

### **Noxious Stimuli**

Environmental noise, lights, loud conversations and nursing activities have been reported to increase ICP in some patients, particularly those with minimal reserves of

intracranial compliance. It is important that the nurse monitor if ICP and CPP increases during nursing care activities and be prepared to stop and place the patient in a neutral position if the ICP increases above a level predetermined by the physician (26).

The nurse must monitor the environment to protect the patient from excessive stimulation and plan and organize patient care to assure that nursing procedures (i.e. turning positioning, bathing, oral care, suctioning) are done in a manner that minimizes noxious stimulation to the degree possible. It is also important for the nurse to educate the family regarding the effects of noxious stimuli (6, 14, 26).

### **Clinical Pathways**

Protocols and clinical pathways are valuable clinical tools which describe observable and measurable outcomes with specified time frames and provide an organized, systematic model for analysis of trends which require intervention by various members of the interdisciplinary team (6, 13, 26). Mcilvoy (41), in a study of the effect of implementing a TBI clinical pathway at a level one trauma center, noted decreases in hospital length of stay and reduction in costs.

### **Family Dynamics/Supportive Interventions in the ICU**

The concept of family focused nursing in the ICU is based on the premise that the family is the primary unit of health care and the patient is best understood within the context of the family system rather than in isolation. It is essential that communication occur with the family/significant others as early as possible. Loved ones can provide pertinent information about the patient's preinjury medical history and, if present, details surrounding the events preceding the TBI. Also, the patient emerging from coma may demonstrate less confusion/agitation in the presence of a loved one (42–44).

The need for medical information was identified as a priority in several studies which investigated the needs of family members whose loved ones sustained a brain injury (44–46). Ideally, the nurse should be present when the physician discusses the patient's medical condition and prognosis with the family (44, 47). The nurse can then reinforce this information in a caring manner with kind, clear, realistic explanations of the patient's medical condition.

Because of the severe nature of TBI, the family of the injured person often demonstrates symptoms of shock, disbelief, denial, anxiety, and anger. This anger can be displaced onto the nursing staff, since it is the nursing staff who provide care around the clock and have more contact with the families than other health care professionals (45).

Hainesworth (48), in a study of acute care nurses caring for neurologically devastated patients, reported that nurses expressed feelings of severe stress and anxiety when they had to endure verbal and occasional physical outbursts from family members. Villaneuva (49) and Bell (50) reported that the experience level of the nurse and the responsiveness of the patient accounted for many of the variations of how nurses interact with patients and families. For some nurses, particularly novice ones, the technical care in of itself can be overwhelming and the nurse, if not provided with support, may have a tendency to focus more on the technological aspects of care and less on the patient as a person.

Educational instruction specific to family dynamics, the recovery process, and strategies for intervention should be an integral part of the training that nurses receive. Villanueva (49) stressed the importance of experienced nurses serving as role models in the sharing and teaching of the knowledge they have acquired to help ease the transition of the new nurse. The nurse's inclusion as part of the interdisciplinary team also serves to allay a sense of isolation and provides a consistent, consensual approach to dealing with family members who are demonstrating challenging interpersonal interactions.

### **Rehabilitation Services in the ICU**

The initiation of interdisciplinary rehabilitative services in the ICU should begin once it is determined that sufficient medical stabilization has occurred (51, 52). A 1992 study by MacKay et al. (53) assessed the occupational and long-term benefits of a formal early intervention program which provided physical, occupational and speech-language therapy services to a group of patients two days after admission compared with a nonformalized group who received rehabilitation services after an average of twenty three days into their hospital stay. The study demonstrated a dramatic reduction in inpatient (acute care and rehabilitation facility) length of stay in the formalized intervention group from 10 months to 5 months. Ninety-four percent of the patients from the formalized group were able to be discharged home as compared with fifty seven percent from the nonformalized group.

### **ACUTE/SUBACUTE REHABILITATION**

Due to increasingly shortened lengths of stay in the acute care hospital, patients are being discharged sooner to acute/sub-acute settings with multiple medical complications and neuropsychological sequela. The intent of this section is to provide a concise multi-system overview that briefly outlines the nursing care issues most commonly encountered. The reader is referred to the other chapters in this text for in-depth discussions.

### **Care of Persons in Low-Level Neurologic States**

The goals of nursing management for patients functioning at the Rancho Los Amigos Levels I, II and III who are admitted to an acute/subacute rehab facility are the same as in the acute care hospital. The Rancho Los Amigos Levels of Cognitive Function scale, while less valid and reliable than the Disability Rating Scale and other outcome measurement tools, is useful as a descriptive tool to categorize behavioral criteria that describe the patient's level of awareness and capacity to appropriately interact with the environment (54, 55).

Nursing staff are in an ideal position to observe spontaneous eye opening, purposeful versus nonpurposeful movement, the person's cognitive/behavioral level of responsiveness to stimulation and commands and the return of sleep-wake cycles. It is important that nurses understand the definitions and diagnostic criteria for the various disorders of consciousness (e.g. coma, vegetative state, minimally conscious state) (56).

After a diagnosis has been established, and consideration given to the etiology and location of injury, length of time since injury, comorbidity of medical complications, age, and knowledge of the patient's wishes, the physician may choose to discuss treatment alternatives (i.e. do not resuscitate (DNR) orders, mechanical ventilation, dialysis, administration of blood/ blood products, the administration of antibiotics and other medications, artificial hydration/nutrition) with the family/decision maker (57-59).

The nurse will be directly involved in supporting the family/decision maker throughout this process. It is, therefore, helpful to have the nurse present whenever the physician discusses these treatment alternatives. In addition to the medical rationale underlying treatment alternatives, the nurse must be cognizant of the legal and ethical policies of the health care facility and the need for compliance with state laws (statutory or court recognized) regarding advance directives (60).

Factors to consider include the emotional readiness of the family, the prognosis for functional recovery (56, 57, 59), (See other chapters for detailed prognostic information) and, most importantly, respect for the patient's wishes. Religious and cultural beliefs and the family's feeling of needing to deal with "unfinished business" all impact on this process.

### **Sensory/Environmental Stimulation of Persons in Low-Level Neurological States**

Persons may present to the rehab setting from the ICU with orders for multiple medications (e.g., anticonvulsants, benzodiazepines, narcotics, antihistamines, neuroleptics, antispasticity agents, gastrointestinal agents, anticholinergics, antiemetics, hypnotics) that may potentially impair recovery. As medications that can potentially

impair arousal are discontinued and cognitive enhancing medications initiated, the nurse must objectively observe the patient's level of neurobehavioral responsiveness, recognize potential side effects and promptly report objective assessment findings to the physician and the interdisciplinary team (59).

While caring for the patient, the nurse should be respectful of the possibility that the patient may be able to hear and possibly understand what is being said. The nurse should always address the patient by name, provide simple reality orientation to person, time and place and always talk calmly in a clear and concise manner to prepare the patient for what procedure or treatment is going to next occur (6, 61, 62).

The nurse can encourage the family to interact with their loved one through therapeutic touch, hand-holding and passive range of motion exercises, if clinically appropriate. Bringing in familiar objects from home and playing music and television programs that the patient enjoyed may provide meaningful visual and auditory stimulation. If the person begins to follow even one step verbal or written commands, a simple communication system can be established with head nods, eye blinks, up and down eye movements, or finger raising yes-no signals (6, 61, 62).

The nurse should educate the family regarding the importance of preventing over stimulation and alert the family that possible causes of restlessness may include pain, irritation from tubes/positioning devices, full bladder/bowel, constipation and other noxious stimuli (6, 61).

### *Respiratory Abnormalities*

Clinical conditions which can increase the propensity toward respiratory complications include chest trauma, weakened or absent gag reflex, dysfunction of the lower esophageal sphincter, dysphagia, ineffective airway clearance, aspiration, recurrent regurgitation, and decreased mobility (61, 63–65). Bontke et al. (63) in a study of rehabilitation patients in the TBI Model System Programs identified respiratory failure (defined as requiring artificial ventilation for more than one week) in 39% of cases followed by pneumonitis (26%) as the most common extracerebral complications seen after brain injury.

Monitoring for a patent airway, rate, depth and pattern of respirations, auscultation for breath sounds, assessment of cough reflex, turning and positioning every one to two hours to mobilize secretions, humidification and suctioning are critical nursing interventions. Secretions should be observed for viscosity, color and odor (6, 61). Decannulation protocols may be initiated when deemed clinically appropriate, but in the low level patient, an individual risk versus benefit decision must be made regarding the suppressed ability to cough and clear secretions versus complications from long-term tracheostomies (59, 63, 64).

Aspiration is a major cause of pneumonia. Unless clinically contraindicated, the head of the bed should be maintained at 30–45 degrees. To prevent aspiration associated with enteral feedings, an initial swallowing study should be performed with high-risk patients, correct placement of feeding tubes monitored, gastric residuals routinely checked, stomach contents aspirated to determine gastric pH, and ongoing assessment performed of the benefit/risk of continuous versus intermittent feedings (65).

### *Cardiovascular Abnormalities*

Life-threatening arrhythmias, changes in cardiac rate and conduction, and alterations in blood pressure may be neurogenic in origin and can occur during the acute/subacute rehab stay. The nurse should ongoingly perform a comprehensive cardiovascular assessment which includes the monitoring of vital signs and the rate, rhythm and quality of apical pulses. An admission ECG can serve as baseline to determine changes in cardiac status (6, 16, 68, 69).

Post traumatic hypertension can resolve spontaneously. Labi and Horn (68) reported that only 45% of persons who had been receiving antihypertensive medications during their rehabilitation stay, required them at the time of discharge. It is important that the nurse keep the physician apprised of blood pressure readings so that a determination can be made by the physician regarding the appropriateness of weaning and/or discontinuing these medications, particularly those with sedating and central nervous system side effects, which could impair recovery (69).

After major brain trauma, the incidence of deep venous thrombosis (DVT) has been reported to be as high as 54% (69, 70). The nurse should monitor vital signs, assess peripheral pulses and Homans'sign, perform bilateral circumferential leg measurements, and examine extremities for redness, pain, tenderness, edema, and dilated superficial veins. DVT and pulmonary embolism may occur, however, without warning thereby making prophylaxis essential (71).

Compression stockings are mechanical methods of prophylaxis and should be fitted in accordance with the manufacturer's sizing chart. Stockings which are too large will not provide adequate support to the extremities and stockings too small may cause circulatory impairment. The patient's legs should be elevated prior to application, wrinkles in the stockings avoided and the patient observed for allergic reactions, skin irritation and thrombophlebitis (72).

Pneumatic compression boots are also used as a mechanical prophylaxis to DVT; however, the boots must be applied in accordance with manufacturer's instructions. Camerota et al. (73) reported that only 48% of patients in an acute care facility and 33% in a nursing home had the boots correctly applied.

Several studies (66, 74, 75) have reported a greater reduction in the incidence of thromboembolic events when pneumatic compression boots were used in combination with anticoagulant therapy. The use of anticoagulant therapy; however, requires a case specific risk versus benefit determination by the physician (66, 69).

### *Genitourinary Abnormalities*

Urinary elimination patterns are frequently altered after brain injury. Patients typically present with uninhibited detrusor hyperreflexia (e.g. spastic bladder), and demonstrate symptoms of urge incontinence which include urgency, frequency, decreased bladder capacity, normal bladder sensation and normal to low post void residuals (61, 76).

Other types of incontinence (i.e. stress, reflex, functional, overflow, mixed) may also occur secondary to urinary retention, pudendal nerve damage, trauma to the urinary tract, benign prostatic hypertrophy, spinal cord injury, or cognitive impairment (62, 69, 76–78).

Transient causes of incontinence which need to be ruled out may include delirium, UTI's, atrophic urethritis or vaginitis, impaction, restricted mobility and even depression. Excess urine output can also be related to endocrine problems, hyperglycemia, hypercalcemia, congestive heart failure and peripheral edema (77, 79). Cognitive and behavioral disturbances, lack of initiation, decreased awareness, agitation, confusion, disorientation, communication and mobility issues also may contribute to incontinence (78, 79).

Medications such as benzodiazepines may cause confusion and secondary incontinence. Diuretics may lead to incontinence due to polyuria, frequency and urgency. Anticholinergic agents (including antihistamines, antidepressants, antipsychotics, opiates, antispasmodics, anti-parkinsonian agents), alpha-adrenergic agonists (such as those found in over the counter decongestants and diet pills), beta-adrenergic agonists and calcium-channel blockers may also cause urinary retention and overflow incontinence (77).

Persons often enter the acute/subacute rehab setting with indwelling urethral catheters. A study by Yost (80) reported the development of urinary tract infections (UTI's) within 72 hours of first use in 70% of the patients studied. Additional complications from indwelling catheters may include hematuria, obstruction, pain, bladder spasms, urethral erosion, stones, epididymitis, periurethral abscess, fistula formation, chronic renal inflammation, bacteremia and pyelonephritis (77–79).

In June of 2005, the Centers for Medicare and Medicaid Services (CMS) released a revision to the State Operations Manual (SOM) specific to Surveyor Guidance for Incontinence and Catheters. This memorandum specifies that an assessment for the appropriateness of an

indwelling catheter should be performed on admission and ongoingly and catheter use restricted to: (1) urinary retention that cannot be treated or medically/surgically corrected (i.e. post void residual volumes over 200 milliliters, unsuccessful management of retention/incontinence with intermittent catheterization and persistent overflow incontinence, symptomatic infections and/or renal dysfunction), (2) the need to prevent further contamination of Stage III or Stage IV pressure ulcers or (3) use as a comfort measure in terminally ill patients where changing is painful and disruptive (78).

The first step in assuring that the patient with bladder incontinence receives appropriate treatment to prevent UTI's and restore bladder function, is the performance of a thorough assessment. Discussion with the patient/family should occur prior to starting a bladder management program and information obtained specific to previous elimination patterns and pre-morbid urinary tract complications. A pelvic and rectal examination should be done to rule out factors which may affect incontinence (i.e. prolapsed uterus or bladder, prostate enlargement, fecal impaction). Several post-void residuals, preferably thru ultrasonographic assessment, should also be obtained to ensure adequate emptying and a cough stress test performed to determine if urine leakage is provoked (77, 78).

The two essential components of a bladder program are a schedule of fluid management and a pre-established voiding schedule. Unless clinically contraindicated, overhydrating in the morning and early afternoon serves to cue the patient to a sensation of a full bladder. To promote rest, fluids are restricted after 7p.m. (especially caffeinated drinks). The fluid needs for an average person is 2500cc per 24 hour period but may vary depending on clinical variables (77–79).

Programs range from care-giver dependent (scheduled check and change) to those requiring active patient involvement. "Habit training/scheduled voiding," a behavioral technique whereby toileting is scheduled to coincide with a predetermined analysis of the patient's voiding patterns and times of fluid intake, can begin when the person is cognitively functioning at Rancho Level V (77–79).

"Prompted voiding" may be appropriate with patients who can recognize some degree of bladder fullness, ask for assistance or are able to respond to the staff when prompted to toilet. The patient receives positive feedback if they void successfully when prompted or remain dry after declining toileting. As the program progresses, the patient may learn to recognize the need to void, to ask for help or respond when prompted (77, 78).

In a study involving nursing home residents, a 40% reduction in incontinent episodes occurred in response to prompted voiding techniques regardless of the type of urinary incontinence or cognitive deficit (residents were able to say their name or reliably point to one of two objects) (81).

“Bladder rehabilitation/bladder retraining” is appropriate for cognitively intact patients and requires the capability to delay voiding and to urinate according to a timetable. Based on the baseline assessment of voiding times, the person is encouraged to lengthen the time between voids by consciously suppressing the urge. Bladder training can also be combined with pelvic muscle (Kegel) exercises and pelvic floor electrical stimulation therapy (77, 78). A cystometrogram EMG is sometimes done to determine the patient’s degree of sensation and voluntary control (54).

Most importantly, the success of bladder programs requires the commitment and compliance of the direct care staff to implement the program and the support of administrative staff to provide adequate numbers of staff.

Anticholinergic medications are sometimes used to relax smooth muscle in the urinary tract, increase bladder capacity and increase the threshold volume for overactive bladder contractions. Caution is advised, however, due to side effects such as urinary retention, sedation and memory impairment (54, 66). Anticholinergics are contraindicated in patients with narrow-angle glaucoma (77).

Male external collection devices (i.e. condom catheters) are available, but also are associated with increased risk of UTI’s (82). Patients must be carefully evaluated prior to use for symptomatic UTI, urinary retention and upper tract damage. These devices should not be used in patients with chronic obstruction. Proper application is critical and the patient must be routinely monitored for contact dermatitis, maceration and irritation of the penis, ischemia, penile obstruction and UTI (61, 77, 78).

External collection devices for females are not widely used. Reported adverse reactions include periurethral erythema, perineal itching, skin abrasions, and adherence problems (77, 78, 83). Incontinence briefs are typically used in females. After each episode of incontinence, the skin should be checked for breakdown, a moisture barrier applied and the skin kept clean and dry.

### *Gastrointestinal Abnormalities*

After TBI, the patient is at risk for the development of gastritis, duodenitis, gastroparesis, lower esophageal sphincter dysfunction, gastric atony, and stress ulcers (74). Gastrointestinal bleeding is a serious complication which has been reported in up to 80% of patients who have sustained TBI’s (84). Medications such as steroids, nonsteroidal anti-inflammatory agents, aspirin and anti-coagulants may also exacerbate the problem due to their propensity to increase GI bleeding (66).

Antacids, H<sub>2</sub> blockers, or sucralfate may be used prophylactically in the acute phase after TBI; (74, 85) however, the patient must be closely monitored due to the increased risk of pneumonia which has been reported with the use of antacids or H<sub>2</sub> blockers (86, 87).

Metoclopramide, a central dopamine receptor antagonist, has been historically used to treat gastroparesis and gastroesophageal reflux but observation must occur for deleterious effects such as sedation and extrapyramidal symptoms (54, 87, 88).

A gastrointestinal assessment should include auscultation of the abdomen in all four quadrants for bowel sounds, palpation for signs of pain or distention, testing of stool for occult blood and monitoring vital signs and serial Hgb and Hct for changes indicative of hemorrhage. Checking stool for frequency, color and consistency is important due to the predisposition for constipation secondary to immobility, opiates and fluid restrictions. Conversely, diarrhea may occur due to intolerance to tube feeding or antibiotics (61). Other serious bowel complications include, impaction, intestinal obstruction, paralytic ileus and clostridium difficile colitis (16, 26, 76).

After brain injury, bowel incontinence typically occurs secondary to upper motor neuron damage which results in uninhibited neurogenic bowel; however, co-existing spinal cord and traumatic injuries and preexisting gastrointestinal diseases can also effect bowel continence. Prior to implementation of a bowel program, it is important to determine the type/s of neurogenic bowel dysfunction. A rectal exam should be performed to assess the condition of external and internal hemorrhoids and a physical assessment done to determine if saddle sensation, the bulbocavernosus and anal reflexes are intact (76, 89).

Discussion should occur with the family to determine preexisting elimination patterns and a baseline assessment conducted to determine the time of day and frequency of stools. Based on identified patterns, a toileting schedule can be developed preferably 15–30 minutes after meals, to facilitate the effect of the gastrocolic reflex. Unless clinically contraindicated, left side-lying or sitting will also facilitate evacuation. Adequate fluid intake and close monitoring of tube feeding to assure adequate amounts of fiber, roughage and fluid is also important (61, 76, 89).

Stool softeners and bulk formers should be utilized and dosages and times of administration adjusted as needed. Digital stimulation is not appropriate in bowel programs to manage uninhibited neurogenic bowel, but suppositories or products such as Theravac SB™, a 4cm<sup>3</sup> mini-enema/stool softener laxative may be used to trigger the defecation reflex. A daily bowel movement is not necessary but a patient should not go for more than 3 days without a bowel movement. Continuity of the program is maintained even if the patient has a bowel movement between training times (61, 76, 89, 90).

### *Nutrition and Feeding*

In a study of patients admitted to a rehabilitation unit, Brooke and Barbour (91) reported an average weight loss of 29 pounds. The need for increased nutritional support

can persist indefinitely in the rehabilitation setting and is exacerbated by medical problems such as fever, pressure sores, infection, spasticity, dehydration and loss of fluid due to wound drainage, excessive sweating and diarrhea (91, 92).

An accurate weight should be taken the day of admission and afterward, at the frequency specified by the physician or dietician. Due to problems with scale calibrations, accuracy, and inconsistencies in obtaining timely weights, it is helpful if a small number of designated staff members obtain weights using the same scale and at the same time of day. A system should be in place to assure prompt notification and follow-up by the physician and dietician. Nutritional deficiencies should also be discussed at the interdisciplinary team meeting.

Percutaneous endoscopic gastrostomy (PEG) tubes are commonly utilized in the rehab setting, particularly when long-term nutritional support is anticipated. Prior to administering feedings/medications an abdominal assessment and auscultation of bowel sounds should be performed and tube placement confirmed by checking gastric residuals and the pH of gastric contents per facility policy (72). Feeding tubes should be clamped for at least 30 minutes (or longer per pharmacist recommendations) after phenytoin administration to facilitate absorption, as noted in a study by Faraji et al. (93) who reported a decrease in available phenytoin blood levels when given with tube feeding.

To minimize the risk of aspiration, the head of the bed should be elevated 30–45 degrees. Observation of skin integrity at the stoma site is important since irritation and excoriation can occur due to leakage of gastric secretions (72). The decision to discontinue enteral feeding is dependent upon many factors including the functional integrity of reflexive and voluntary components of oral motor function, the person's level of arousal, the successful management of dysphagia, the degree of facial trauma, and the stability of the patient's nutritional status (37, 54) (Please note: see the chapter on gastrointestinal and nutritional issues and neurogenic swallowing disorders for more detailed information).

### *Spasticity and Musculoskeletal Complications*

Upon admission to the acute/subacute unit it is important to get a detailed history of the trauma that the person sustained. Fractures occur in approximately 30% of persons who have sustained a TBI, (94) 11%, of which are undiagnosed at the time of admission to a rehab setting (95). Peripheral nerve injuries occur in 34% of severely injured TBI patients with 11% also undiagnosed at the time of admission (95). The nurse should routinely assess for unexplained swelling, discoloration, deformity, pain, limitation of range of motion, and, particularly for, signs and symptoms of spinal fractures. Early fracture

fixation is typically performed which facilitates a shorter period of immobilization, earlier range of motion, and fewer problems with pain, contractures, pulmonary complications, severe spasticity and ankylosing heterotopic ossification (69).

The greatest risk for the development of heterotopic ossification (HO) is in the first 3–4 months after injury (69). Unfortunately, the process begins before clinical symptoms are observable. The nurse must be vigilant in observing for decreased range of motion in the affected joint, swelling, warmth, erythema, pain, fever and contracture formation. Range of motion exercises, physical therapy, medications and orthotic devices may be implemented both prophylactically and as a component of treatment at the physician's discretion (66, 96). Surgery may be an option 12–18 months post-injury if significant functional limitation due to deformity is present (54, 66).

Muscle tone abnormalities, flaccidity, rigidity, spasticity, dystonia, paresis, paralysis, contractures, decorticate and decerebrate posturing may be seen after a person has sustained a TBI (66, 69, 97). Nurses should be knowledgeable in performing a basic assessment of tone. The Ashworth and/or Modified Ashworth Scale which grades the degree of hypertonicity in muscle, can be easily learned and facilitates the nurse's reporting of objective input regarding the presence of spasticity (92, 97, 98).

Interdisciplinary collaboration between the physiatrist, PT, OT and nursing staff is critical. Nursing is directly involved in carry over with many treatment modalities. Specific feedback and hands-on instruction should be received from the physical or occupational therapist in regard to specific range of motion exercises, wheelchair and bed positioning programs and splinting interventions (61, 99). When orthotic or splinting devices are used, it is imperative that the nurse assure that adherence to off/on wearing schedules is maintained, neurological and vascular status monitored, and skin observed for breakdown (61).

Nurses need to provide a calm environment for patients with muscle tone abnormalities. Noxious stimuli which can trigger an increase in spasticity include: pain, fear, anxiety, irritation from tubes/positioning devices, DVT, full bladder/bowel, constipation, urinary tract infection, HO, skin breakdown, tight clothing or even the need for repositioning (98, 100).

Systemic pharmacological agents such as diazepam, baclofen, dantrolene sodium, clonidine, and tizanidine hydrochloride are sometimes prescribed but the literature regarding the benefits in treating spasticity of cerebral origin is limited (99). Nurses need to be astute in monitoring any appreciable improvement in tone versus the potentially negative effects on cognition from the use of these medications.

It is also important that protocols be established so that nurses can systematically assess the side effects and



potential complications that can arise after botulinum toxin injections, chemoneurolytic nerve blocks and intrathecal baclofen therapy (100, 101) (Please note: see the chapter on spasticity and musculoskeletal complications for more specific information).

### *Skin Care*

Although not widely discussed in the TBI literature, the failure to maintain the integrity of the patient's skin presents significant morbidity and mortality risks. The new pressure ulcer guidelines released on November 12, 2004 by the Centers for Medicare and Medicaid Services (CMS) provide a comprehensive and instructive guideline which reflect current best practices specific to the prevention and treatment of pressure ulcers (102).

A pressure ulcer is defined by the National Pressure Ulcer Advisory Panel (NPUAP) as "any lesion caused by unrelieved pressure resulting in damage of underlying tissue" (102–104). Pressure ulcers occur when soft tissue is

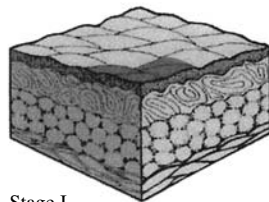
compressed between a bony prominence and an external surface and can develop within 2–6 hours of the onset of pressure (105). The most common sites and distribution frequency include the sacrum (36–49%), heels (19–36%), ischium (6–16%), trochanter (6–11%), and malleolus (7–8%) (106). Pressure ulcers may lead to pain, increased risk of complications, increased length of stay, staggering costs and interference with rehabilitation interventions and ultimate recovery (107, 108).

Pressure ulcers, as defined by the NPUAP, are staged to classify the degree of tissue damage and range from Stage I, "an observable pressure-related alteration of intact skin" (i.e. change in skin temperature, tissue consistency, sensation or persistent redness or change in coloration) which persists 30–45 minutes after pressure is removed to Stage IV which is defined as full thickness skin loss with extensive destruction, tissue necrosis or damage to muscle, bone or supporting structures (102–104) (See Figure 40-1) Although the nurse is primarily responsible for assessment and treatment of pressure ulcers,

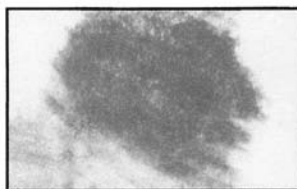
## ***The NPUAP Pressure Ulcer Staging System\****

### ***Stage I***

Nonblanchable erythema of intact skin, the heralding lesion of skin ulceration. In individuals with darker skin, discoloration of the skin, warmth, edema, induration or hardness may also be indicators.

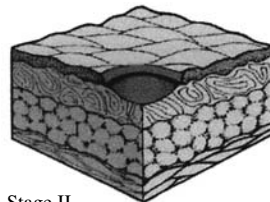


Stage I.

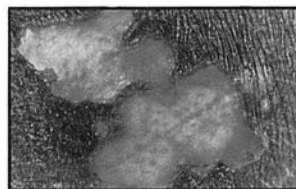


### ***Stage II***

Partial-thickness skin loss involving epidermis, dermis, or both. The ulcer is superficial and presents clinically as an abrasion, blister or shallow crater.

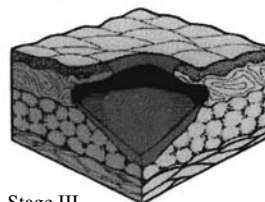


Stage II.

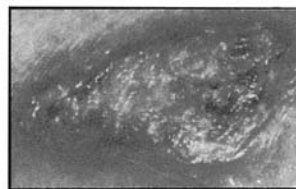


### ***Stage III***

Full thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to, but not through, underlying fascia. The ulcer presents clinically as a deep crater with or without undermining of adjacent tissue.

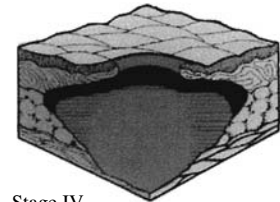


Stage III.

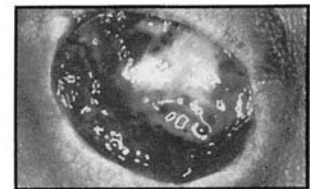


### ***Stage IV***

Full thickness skin loss with extensive destruction, tissue necrosis, or damage to muscle, bone or supporting structures (e.g., tendon, joint capsule). Undermining and sinus tracts also may be associated with Stage IV ulcers.



Stage IV.



- Stage I ulcers may not always be diagnosed reliably in patients with darkly pigmented skin.
- When eschar is present, a pressure ulcer cannot be staged accurately until the eschar is removed.
- Be alert to pressure-induced pain in patients with casts or support stockings.

**FIGURE 40-1**

the maintenance of skin integrity is accomplished thru a team approach and all members of the interdisciplinary team need to clearly understand risk assessment, wound staging, and preventive protocols.

Identification of risk factors is the first step toward prevention of pressure ulcers. After TBI, patients have a multitude of factors which place them at significant risk for the development of pressure ulcers including: (1) immobility, (2) orthopedic, neurological and vascular trauma, (3) infection, (4) altered sensorium, (5) malnutrition (dehydration, hypoproteinemia, anemia, vitamin deficiency), (6) musculoskeletal alterations (spasticity, contractures, loss of subcutaneous tissue, muscle atrophy, flaccidity), (7) bowel and bladder incontinence, (8) pain, (9) orthopedic procedures of the hip and femur, (10) medications (narcotics, sedative, analgesics, steroids), (11) decreased sensory impairment, (12) diaphoresis, (13) metabolic disturbances, and (14) external mechanical forces (i.e. pressure, friction and shear, casts, splints, orthoses, braces, fixation and positioning devices) (61, 102–104, 108).

Preventive interventions begin with an initial and ongoing completion of a validated risk assessment tool such as the Braden Scale to identify specific factors which place the patient at risk (i.e. sensory perception, moisture, activity, mobility, nutrition, friction and sheer) for the development of pressure ulcers (103, 104).

A comprehensive interdisciplinary care plan is then developed which includes: (1) a protocol for systematic total skin inspection once per day, paying particular attention to bony prominences, (2) proper bed and wheelchair positioning, (3) appropriate transferring to minimize skin injury due to friction and shear, (4) nutritional interventions to assure adequate food and fluid intake to prevent weight loss and malnutrition, (5) incontinence care followed by antibacterial, moisture barrier ointment, (6) pressure reducing seating cushions, (7) written, patient specific, turning and positioning schedules (8) pillows/devices which relieve pressure on the heels and (9) pain management (102–104, 108).

A patient specific assessment (i.e. ability to maintain position, multiple pressure ulcers, limited turning surfaces) must also be conducted to determine the most clinically appropriate support surface (i.e. pressure reduction versus pressure relief, dynamic versus static air or fluid support) and the type of device used (i.e. overlay, replacement mattress or specialty bed) (102, 104, 108).

Wound cleansing should occur with normal saline with enough irrigation pressure to enhance cleansing without causing wound bed trauma. Skin cleansers or antiseptic agents (e.g. povidone iodine, iodophor, Dakin's, hydrogen peroxide and acetic acid) are cytotoxic to normal tissue and should not be used (103, 104).

Treatment of a pressure ulcer begins with an accurate assessment of the ulcer itself specific to size, depth, edges, undermining/tunneling, location, stage, necrotic tissue,

type, color, odor and amount of exudate, skin condition surrounding the wound, granulation tissue, infection and pain (102–104).

If it is determined that debridement (sharp, mechanical, enzymatic and/or autolytic) is necessary, a decision must be made regarding the most appropriate debridement modality. It is important to note that heel ulcers with dry eschar that is clean, dry, nontender, nonfluctuant, nonerythematous and nonsuppurative need not be debrided (102, 103, 108).

Dressings are required to maintain the physiologic integrity of the pressure ulcer. The wound must be protected, the ulcer bed kept continuously moist and the surrounding intact (periulcer) skin kept dry. Moist wound dressings prevent dessication. Drying out a wound destroys healthy tissue and can lead to eschar, infection, and impaired healing. Moist wound dressings promote wound healing through an autolytic process which prevents damage to new cells while debriding the wound, but balance is needed to assure that healing is not impeded due to excessive wound exudate (102–104, 108). Wet to dry dressings should be used only in limited circumstances due to the risk of damaging healthy granulation tissue and causing excessive bleeding and pain (102).

The decision as to which wound care products (i.e. transparent films, hydrogels, hydrocolloids, alginates, foams, composite dressings,) to use should be made based on the previously noted treatment assessment factors. Other factors to consider include cost, and the time involved for the staff to perform the dressing change. Ongoing assessment and interventions for pain is paramount (102–104, 108).

If the pressure ulcer does not demonstrate healing progress within 2–4 weeks, the treatment plan/protocol and the patient's overall condition should be reassessed (102, 104). Pressure ulcer related complications include cellulitis, osteomyelitis, septic arthritis, abscess, bacteremia, septicemia and chronic infection (102–104).

Adjunctive therapies that may enhance pressure ulcer healing include electrical stimulation, vacuum assisted closure (VAC), and surgical intervention (flap) (108).

Ongoing training and education should be conducted by a nurse with recognized training and education in pressure ulcer management and directed toward all members of the interdisciplinary team and the family.

### *Family Dynamics/Supportive Interventions*

Rosen (109) studied the reactions of families whose loved ones remained in a vegetative state and described a five component model which included: (1) grief and anxiety, (2) guilt, (3) denial, (4) accommodation, and (5) disengagement and rejection. The reactions of family members have been described as dynamic, intense and disorganized with family members experiencing several reactions at the

same time and not moving through the stages in any predetermined fashion (43, 110).

Families may report feeling that they are in a state of “limbo”. Spontaneous and reflexive movements may be perceived by the family that the person recognizes them and is trying to awaken. The person is physically present yet what is gone, perhaps forever, is the person who they actually were. The uncertainty as to the likelihood of any further improvement, the guilt of “abandoning hope”, the strain of being pulled in different directions by other family members and work commitments, and the financial burdens all give rise to the family’s experiencing severe stress reactions (43, 61, 110, 111).

The family may displace feelings of anger, frustration and rage onto the nursing staff in the form of excessive criticism, blame, unrealistic demands, inappropriate emphasis on minor aspects of care, and extended vigils at the bedside (43, 61, 110–112). Families have even been observed to display hostility and open aggression directed toward the staff, a reaction described by Stern (113) as relatively unique to families with loved ones in prolonged low level neurological states exceeding four months.

It is imperative that nurses be active participants in the interdisciplinary team’s establishment of a family plan of care which acknowledges the dynamics behind the family’s responses to their loved one’s injury. Only then can specific therapeutic interventions be developed which assist the family to positively participate in the rehabilitation process (43).

### POST-ACUTE COGNITIVE NEUROBEHAVIORAL REHABILITATION

This chapter has thus far focused primarily on the physical impairments sustained after TBI. It is, however, the cognitive, psychosocial and neurobehavioral problems following TBI that can most profoundly affect the person’s response to rehabilitative intervention, their interpersonal relationships and their successful reintegration into the community (114, 115). It is the treatment of these sequelae that often poses the greatest challenge to the nursing staff caring for persons who have sustained TBI’s.

In a rehabilitation setting, a nurse is often the senior clinician with twenty-four hour responsibility for assuring that care plan approaches for intervening with a person’s maladaptive and sometimes dangerous behaviors are consistently implemented and that the patients, staff, family members and visitors are kept safe. Nurses, however, receive only limited training in their nursing education to prepare them to effectively manage behavioral sequelae or to effectively supervise licensed and paraprofessional staff members in the implementation of therapeutic interventions. This can be particularly problematic during off-shifts and weekends when staffing is likely to

be the most minimal and support persons are not immediately available (116).

The primary focus of this section will be the pragmatic aspects of the nurse’s role in maintaining a therapeutic milieu for the treatment of patients demonstrating behavioral issues after TBI. Neuropsychological assessment and psychopharmacological intervention will be addressed elsewhere in this text.

### Assessment

It is important that the nurse interview the family member/significant others. This comprehensive assessment must include a review of the patient’s premorbid level of cognitive abilities, strengths and weaknesses. Factors which can influence cognitive and behavioral manifestations of behavior include injury severity, age, early developmental factors, time post injury, diffuse versus focal or combined injuries, length of coma, and length of amnesia. Premorbid patient variables such as education, occupation, psychiatric conditions, substance abuse problems and previous brain injury can also impact prognosis (117).

Although an extensive cognitive and neurobehavioral assessment will most likely be performed by the neuropsychologist, nurses may be involved in administering simple tests such as the Folstein Mini-Mental Status Examination which provides specific, detailed and useful information regarding the patient’s orientation, insight, recall, attention, visual-spatial skills, affect and speech (118).

### Defining Behavior

It is important for the nurse to understand the need for objective, quantifiable, measurable definitions of behavior. Although less statistically valid and reliable than other scales, a cognitive recovery scale still widely used to describe a person’s level of awareness is the Rancho Los Amigos Scale. A person functioning at Rancho Level IV is “confused, agitated-inappropriate” (54, 119).

Descriptive characteristics of Rancho Level IV include: “severely impaired information processing; responding to internal confusion; attention span very limited; behavior often bizarre; short-term memory impaired; dependent in all aspects of care; safety of major concern”. This state of “agitation” may last days, weeks or throughout a person’s life time and can be internally driven or exacerbated by environmental stressors (54, 119).

Simply labeling a person as “agitated” or a “Level IV”, however, does not provide specific, measurable criteria from which treatment decisions can be made. Although studies have cited the prevalence of “post-traumatic agitation” as ranging between 11–50%, (120, 121) the meaning of the term “agitation” is vague, nonspecific and not

consistently defined. Complicating matters further, is the difficulty in evaluating the efficacy of interventions when comparing studies due to this lack of a universal definition (62).

In 1996, the following definition of the term agitation was proposed: “a subtype of delirium occurring during the period of posttraumatic amnesia characterized by excessive behaviors, including some combination of aggression, akathisia (motor restlessness), disinhibition, and emotional lability” (121–123).

It is the precise defining of these “behaviors”, however, that is necessary to assure objective assessment and therapeutic intervention. An individualized analysis of the individual’s behavior should be conducted and specific descriptors identified based on an operational definition developed by the interdisciplinary team. The Agitated Behavior Scale or the Overt Aggression Scale provide particularly useful behavioral descriptors to assist in targeting specific behaviors (124, 125).

### A–B–C Data

Once a target behavior is defined, a baseline must be established. Data collection should be instituted which includes antecedents, behaviors, and consequences (ABC). Documentation of the antecedent, the stimulus or event which precedes a behavior, allows identification of potential triggers that precipitate behavioral responses. This information may include time of day, a specific activity, hunger, thirst or sleep deprivation, environmental issues, specific caregiver/family member, or change in routine (126, 127).

Specific behaviors, as previously discussed, must be objectively quantified specific to frequency, duration, latency and intensity of the behavior. Finally, it is important to identify the consequences that follow behavior. A consequence may function as a positive or negative reinforcer which increases the likelihood of behavior or as a punishment which decreases the frequency of behavior (54, 62, 126, 127).

### Interdisciplinary Team

The need for a consistent, cohesive, interdisciplinary team led by the physician is paramount when treating persons with behavioral disorders. The interdisciplinary team determines specific interventions based on analysis of the ABC data with feedback from all members of the interdisciplinary team. Interventions should be formalized into an individualized plan of care with specific long term goals, short term objectives and specific approaches. Both the person with the brain injury and their family should be active participants in this process (116, 127).

Time *must* be allotted to include a nurse and nursing assistant as part of this meeting. Unfortunately, it is the

nurse and nursing assistant who are sometimes “pulled” from attending this meeting due to the need for “coverage on the unit”. If staff members have input into the development of the plan of care, they will be better prepared to implement consistent, structured, therapeutic interventions when they are faced with behavior that may be unpredictable and dangerous (116).

### Behavioral Interventions

Staff members need to understand how fatigue and short term memory deficits affect the person’s behavior. Staff must be taught to distinguish between a behavioral deficit in which the person does not know how to perform a particular behavior versus noncompliance in which a person can perform the behavior but is noncompliant. The team must develop a consistent approach for all staff members to follow which is specific to the patient’s learning style and cognitive awareness (116, 126–129).

Behavioral outbursts can be terrifying since they can present as sudden, unprovoked and violent. If the direct care/nursing staff are not provided with training in appropriate limit setting and deescalation techniques and ongoing support and supervision, they may demonstrate feelings of fear, frustration and helplessness, thus compromising the treatment of the patient and the safety of other patients, staff and visitors (62, 116, 128–130).

Staff must be taught to remain calm yet firm, use direct, simple statements and avoid criticizing or arguing. Redirection, consistency and reinforcement of appropriate behavior is critical. Potentially volatile situations must be defused when they begin rather than waiting until the person becomes violent and out of control. If assaultive behavior is imminent, quick, coordinated action is a team effort. A staff member should not try to deal with a potentially explosive situation alone (62, 127–130).

Contingency management systems, positive reinforcement, stimulus control, social skills training, behavior shaping, self-control techniques, cognitive remediation, redirection, distraction, differential reinforcement and modeling of appropriate behavior are examples of strategies that might be utilized to assist the person in regaining self control (54, 127, 130).

### Environmental Interventions

The control of environmental stimulation is necessary in order to decrease the person’s anxiety, restlessness and irritability and to reestablish sleep/wake cycles. Over stimulation can be caused by aggravating factors in the environment such as noise, clutter, crowding, overhead paging, lighting, room temperature variations, ringing phones, loud televisions/radios, inconsistent scheduling of therapy, too many visitors, or nursing care treatments which provoke tactile defensiveness (62, 128, 131).

The environmental milieu may not be conducive for the management of disruptive behavior. The person may be intermingled on a unit with other patients with a variety of diagnoses who are at varying stages of their own recovery. This is particularly problematic when persons who are severely medically compromised and require intensive medical interventions (i.e. vents, tube-feedings, oxygen, IV's, etc.) are intermingled with patients who are either ambulatory or independently mobile in their wheelchairs.

Environmental stimulation should be reduced to enable the staff and family to better individualize interventions which have a calming effect on the person. If stimuli can not be eliminated, the person may benefit from the use of a protective, monitored room in which the floor and walls are covered with protective padding that would enable the patient to be safely mobile (62, 116).

### Falls

Falls are a potentially catastrophic event, particularly in person's who have already sustained a brain injury. Although much of the research done in the area of fall prevention is in the geriatric and stroke literature, (132–137) persons who have suffered brain injuries, demonstrate a multitude of similar characteristics that could put them at risk for falls including: (1) cardiovascular, neurological (weakness, gait and balance disorders, dizziness) and musculoskeletal sequelae, (2) history of falls, (3) incontinence, (4) visual-perceptual disturbances, (5) pain, (6) cognitive impairments (i.e. confusion, impaired arousal, judgement and memory, motor restlessness, impulsivity) and (7) the use of psychotropic, cardiovascular, anti-hypertensive, and diuretic medications. Environmental/situational hazards (i.e. lighting, slippery floors, clutter) also increase the risk of falls.

Fall prevention interventions should be interdisciplinary and based on an individualized assessment of the person's internal and external risk factors and functional impairment. The environment must also be assessed for potential hazards. Interventions might include chair/bed alarms, low beds, strengthening and balance programs, hip protectors, call bells within reach, increased supervision/appropriate staffing, bowel and bladder programs, patient and family safety education, video monitoring systems, medication monitoring, and environmental modifications (6, 62, 132–136, 138).

The Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) Sentinel Event Alert "Fatal Falls:Lessons for the Future", stresses the need for post-fall investigations to identify and analyze the root causes of falls and suggests risk reduction strategies such as fall prevention education of staff, patients and visitors, low beds, bed alarms, bed alarm checks and tests, and the revision of staffing procedures. Formal fall prevention

protocols provide a consistent, organized approach to managing fall risk in persons who have sustained TBI's.

### Restraints

Physical restraints as defined by the Health Care Financing Administration (139) in 1995, include "any manual method or physical or mechanical device, material, or equipment attached or adjacent to the resident's body that the individual cannot remove easily which restricts freedom of movement or normal access to one's body."

CARF similarly defined physical restraints as "restrictive procedures," including devices that "(1) restrict an individual's movement; (2) restrict an individual's ability to obtain positive reinforcement; and (3) restrict an individual's ability to participate in programs" (140).

Following a TBI, patients may demonstrate severe motor restlessness, lack of safety awareness, impulsivity, the need to exit their bed, and a lack of skills to safely ambulate (141, 142). Historically, the use of physical restraints was an intervention utilized to prevent falls, to ensure that medically necessary tubes remained intact, and to keep patients who were "agitated" or "wandering" under control and "safe". The use of restraints was also justified as a necessary prevention intervention to "prevent being sued" (143–146).

Schleenbaker, (147) for example in 1994, reported that 32.2% of rehabilitation patients were mechanically restrained for an average duration of 17 days during their rehab stay and that TBI was a strong predictor of medical immobilization.

Clinical studies over the past decade, however, have demonstrated that the use of physical restraints does not prevent injury or reduce the risk of falls when alternative interventions are implemented. Ironically, there are numerous adverse physical and psychological effects attributed to the use of restraints including: increased incidence of falls, head trauma due to falls, deconditioning, gait and balance problems, incontinence, contractures, pressure sores, loss of muscle tone and independent mobility, chronic constipation, neurovascular compromise, infections, cognitive decline, psychiatric morbidity and serious injuries. Restraints can also actually worsen agitation and restlessness and the person's desire to free themselves from being "tied down", increasing the risk of serious injurious falls and deaths (138, 139, 143, 148–154).

Restraint-related deaths by asphyxiation have occurred whereby the person is suspended by a restraint (i.e. vest, waist restraint) from the bed or a chair and several deaths have been reported in which persons died trying to escape restraints by setting fire to their restraints (155–158).

As of April 1992, prompted by reports of numerous injuries and deaths involving restraints, health care facilities are required to report restraint related injuries to the manufacturers and restraint-related deaths to the FDA (159).

### Siderails

Bilateral full-length siderails were historically placed in the “up” position to “prevent the patient from falling out of bed.” A siderail, however, may be considered to be a restraint depending on how it is being used for a particular individual. If a side rail impedes desired movement, such as keeping the person from getting out of bed it is considered to be a restraint (143, 160, 161).

Side rail usage has not been shown to significantly reduce the likelihood of falling or of serious injuries. Siderails are not a benign intervention (148). If a person is attempting to get out of bed, the siderail can increase the height of a fall by two feet, thus precipitating a fall from a higher distance with an increased risk of injury (139, 162, 163).

Entrapment hazards are particularly dangerous. Parker and Miles (164) studied 74 deaths caused by bedrails between 1993 and 1996 and determined that 70% occurred when the person was entrapped between the mattress and a rail with their face against the mattress. An additional 18% died when the person’s neck was compressed within the rails and 12% died when trapped by the rails after partially sliding off the bed with subsequent neck flexion or chest compression.

The 1995 FDA Safety Alert: “Entrapment Hazards with Hospital Bed Siderails” (165) and the JCAHO Sentinel Event Alert, “Bed rail-related entrapment deaths” (September 6, 2002) describe interventions such as staff education, assessment of residents for entrapment risk, re-evaluations of beds and mattresses for gaps and openings, and modifications which reduce the risk of entrapment such as retrofit kits, bedrail netting, clear padding and Velcro or anti-skid mats to prevent the mattress from shifting.

### Restraint and Siderail Alternatives

Restraint/siderail alternatives may include bed/chair alarms, bed bumpers, perimeter mattresses, low beds, Vail(beds, mattresses on the floor, wheelchair seating adaptations, anti-tipper bars, trapeze, and transfer pole/bars (62, 116, 143, 160, 166).

Restraint alternatives that may be utilized when a patient attempts to dislodge a gastrostomy tube might include an abdominal binder. Elbow splints or mitts may be an alternative to wrist restraints and sleeve covers for peripheral IV’s may be far less agitating than the use of physical restraints (62, 116, 128).

### Wandering

For persons who are at risk for wandering, the environment must provide a safe, protective setting where the person can safely walk or pace if they need to without the risk of elopement. Some units are specified as locked

units; however, in most settings, a safety beeper may be applied to the person’s ankle or wheelchair that will alert the staff whenever an attempted elopement occurs. If the ankle bracelets are used it is imperative that a system be developed whereby the ankle bracelets are monitored to assure placement and proper functioning (62, 116, 141).

### Staffing

Ongoing training for staff at all levels is imperative. The Training Manual for Certified Brain Injury Specialists (CBIS) from the American Academy for the Certification of Brain Injury Specialists (AACBIS) is a specialized training and certification program which can be used to educate and acknowledge caregivers at multiple levels of involvement (130). Staff working with potentially violent patients should also receive crisis intervention management training.

Adequate numbers of staff who are trained to behaviorally manage noncompliant and maladaptive behavior is imperative. An acuity based staffing system should be used which addresses the needs of this unique population and is sensitive to the need for ongoing readjustment. It is important to have the same primary caregiver to the degree possible. The use of agency staff in the treatment of these individuals can create a break in consistency with potentially damaging outcomes. All disciplines including ancillary personnel such as housekeeping and dietary staff must be knowledgeable of the person’s individualized plan of care.

Administrative support is particularly critical when the team decides that 1:1 observation is necessary. Staff members who serve as “sitters” must be thoroughly oriented to the specific individualized care plan for the person they are observing and be able to effectively communicate both in speaking and in writing since they are with the person constantly and can report the least perceptible changes (141, 167).

Prior to placing a person on one to one observation, goals and specific interventions must be established which include criteria for weaning the person from this intensive level of supervision. Supervision must be provided to keep the patient safe but it is also important to be cognizant of the cost associated with this intervention. A 1999 study by Eastwood and Schechtman (167) reported costs associated with 1 to1 monitoring of \$78,000 per year for each patient monitored.

### Pharmacological Interventions

The decision to use pharmacological intervention is predicated upon a risk versus benefit analysis of the intended therapeutic effect versus an adverse effect that can impede recovery. It is important to differentiate “learned” responses of maladaptive behavior that have been inappropriately reinforced from those that are secondary to

the effects of the injury and biochemical disturbances (115, 127).

Prior to beginning psychopharmacologic interventions, it is important that the physician meet with the nurses and other members of the interdisciplinary team to identify and, when possible, treat underlying conditions (e.g. sleep dysfunction, noxious stimuli, seizure disorders, pain, environmental exposures, infections, metabolic or electrolyte abnormalities, liver or renal dysfunction, nutritional deficiencies, constipation, urinary retention, bowel and bladder incontinence, substance abuse) and superimposed central nervous system changes (i.e. stroke, ischemia, focal vascular deficits) which can dramatically affect a person's behavioral presentation. The person's current medications should also be reviewed to assess for drug related withdrawal effects and all unnecessary medications discontinued or appropriate substitutions made (114, 168, 169).

The presence of premorbid behavioral disorders and psychiatric diagnoses (e.g. post-traumatic stress disorder, major depressive disorder, conversion disorder, adjustment disorder, panic disorder, generalized anxiety disorder, mood disorders, organic brain syndrome) must also be considered prior to deciding to utilize psychoactive medications (169).

Once a decision is made to use psychopharmacologic medications, the nursing staff must be vigilant in observing for both intended effects and possible adverse reactions. Concise, objective information, based on observation of clearly definable behavioral responses combined with knowledge of the patient's comorbid conditions, laboratory data, medication regime and a thorough multi-system assessment, must be reported to the physician so that a clinically sound, judicious decision is made in regard to medication use as opposed to the use of medication for convenience (169).

## CONCLUSION

The rehabilitation nursing management of persons who have sustained TBI's is complex, dynamic and uniquely challenging throughout the continuum of care. Brain injury rehabilitation presents the nurse with a unique opportunity to make a profound difference in the survival, the restoration and the maintenance of optimal health, maximal independence and quality of life in persons who have sustained traumatic brain injuries.

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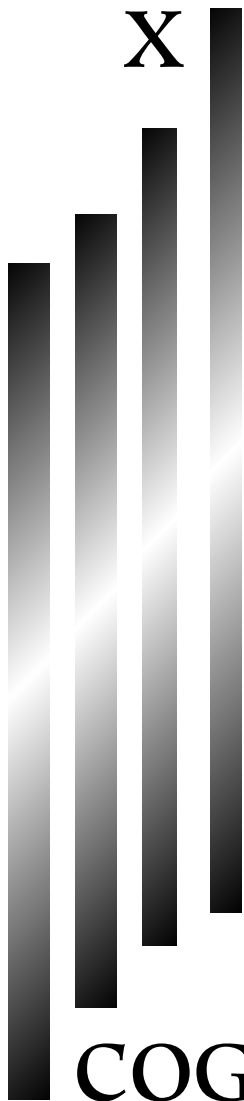
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**COGNITIVE AND  
BEHAVIORAL PROBLEMS**

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# 41

## Cognitive Rehabilitation

*Keith D. Cicerone*

**C**ognitive impairments are often the most persistent and prominent sequelae of brain injury in patients with moderate or good neurologic recovery. Interventions designed to promote the recovery of cognitive functioning and reduce cognitive disability are an integral aspect of brain injury rehabilitation programs after traumatic brain injury (TBI) (1). Despite this, as many as 80% of persons who have sustained a TBI believe that their need to improve their cognition had not been met at one year post-injury (2). The growth in clinical services directed at the rehabilitation of cognitive impairments has recently been matched by efforts to establish the empirical basis for cognitive rehabilitation (3). This chapter is intended to integrate some of the clinical issues involved in the remediation of cognitive impairments after TBI, with a discussion of the empirical literature. The discussion of the literature relies primarily on studies that provide evidence for the “best available practices” in cognitive rehabilitation, but includes some discussion of clinically important or innovative therapies.

### RECOVERY OF NEUROCOGNITIVE FUNCTIONS

In a seminal text on the *Restoration of Function after Brain Injury*, Luria (4) described a number of different

mechanisms to support the re-organization of higher cortical functions after brain injuries. This description rests on the distinction between the two meanings of “function.” The concept of function may be used to refer to the specific activity performed by a tissue or organ; however, in relation to the physiology of higher nervous activity and the psychology of higher cognitive processes, “function” refers to a complex adaptive activity consisting of a group of multistage representations, which are organized in a dynamic relationship, and directed toward performance of a particular task. This conceptualization of function might be better described as a “functional system,” similar to the current concept of distributed cortical networks (5). A fundamental characteristic of a functional system is that different processes may be utilized to carry out a given task under different conditions, a property which increases the adaptability of higher cognitive functions. The mechanisms for recovery of function follow a similar evolution from simple to complex. In cases of damage to the primary cerebral areas serving sensory and motor functioning, re-organization after injury may take place through (a) the ability of intra-systemic processes to take over role of damaged tissue, and (b) the intact influence of higher cortical centers on lower levels of function. At the highest levels of cerebral functional systems, recovery takes place through a process of inter-systemic re-organization, which may include completely different components that formerly served widely different functions.

Luria (4) was eloquent in relating these principles of recovery to specific methods of rehabilitation. He also identified several factors considered to moderate recovery, such as the extent of neurologic damage and the developmental level and premorbid integrity of the disturbed function. One of the principle factors determining the success of restoration of higher cognitive functioning is the patient's level of motivation (or "capacity for mental tension") since recovery at this level requires active, effortful, and conscious compensation.

The neurological mechanisms underlying recovery have continued to receive attention, with several attempts to apply these principles to neurorehabilitation (6, 7). However, few interventions for cognitive impairment after TBI have been derived explicitly from such principles. Current approaches to cognitive rehabilitation do at least implicitly incorporate some of the proposed principles of recovery. Therapies may focus on modification of inherent cognitive processes and abilities, or on the external environmental conditions that affect performance. Therapies may also emphasize retraining of multiple, basic neurocognitive components or the retraining of more integrative abilities and functional skills. Finally, the therapeutic approach can be "bottom-up," based on the sequential building from elementary to complex skills, or "top-down" via the application of superordinate controls over subordinate processes.

### Process-Specific Remediation

Skill-specific or process-specific models of cognitive remediation assume that specific interventions can impact differentially on component neurocognitive deficits. Sohlberg and Mateer (8) developed an influential, process-specific approach to cognitive rehabilitation in which treatments are directed, in highly targeted manner, at specific cognitive areas. The process-specific approach is based on the assumption that direct retraining of specific cognitive processes, through multiple repeated trials of stimulation and activation of the targeted cognitive process, can lead to the reorganization of higher level neurologic and cognitive processes. Treatments are provided in accordance with a hierarchical model of cognitive functioning from lower to higher components of cognitive functioning, in order to provide continuous stimulation and activation of the cognitive process. It is assumed that improvements in functioning at the process-specific level will generalize to tasks that contain similar cognitive requirements, and eventually to improvements in everyday functioning. Gordon and colleagues (9) also combined specific, well-controlled training procedures in basic scanning, somatosensory stimulation and size estimation, and visual-spatial organization into a comprehensive perceptual remediation program. The training program was effective in promoting improvement on psychometric

measures closely related to the training areas. Limited generalization of improvements to measures not specifically related to the training tasks occurred, although the investigators noted more time spent in recreational reading after treatment

### Functional Skills Training

Functional skills training concentrates on the patient's ability in domain-specific, context-specific areas of functioning and the retraining of "competencies of daily life" (10) rather than the putative underlying deficits. Mayer et al. (10) suggested several approaches to training, such as (1) repetition of a whole skill in a natural context (e.g., drinking from a cup during breakfast), (2) training of component parts (e.g., looking for the cup, reaching, grasping, etc) followed by whole-skill training, and (3) various attempts to substitute new procedures to perform the desired activity. Although conceptualizing behavior and presumable interventions according to a hierarchy of pre-skills, individual skills, and routine and activity patterns, this approach did not consider the cognitive task attributes distinct from the functional skills being trained. Following Tsvetkova's (11) notion of retraining within the context of a broader function, they suggest that the remediation of cognitive impairments should not address specific components through training exercises in memory, attention, reasoning, and so on, but to address these impairments only in so far as they are embedded within functional activities. Though the work of Glisky and Schacter (12) is derived from neurocognitive-oriented work on spared memory abilities after brain injury, their training approach is very functionally oriented in its emphasis on the acquisition of domain-specific knowledge by memory-impaired patients. They utilized a method of "vanishing cues" to teach four brain-injured amnesic patients computer-related vocabulary words. Consistent with a functional approach, the training was intended to provide the patients with specific knowledge in an area important to the patient's everyday lives (computer terms) rather than produce general improvements in memory function. Glisky and Schacter (12) suggested that the same procedure might be applied toward the acquisition of complex forms of knowledge by brain-injured patients, as well as the possibility of training patients to become expert in specific, defined content areas. In each of these functional approaches the patient is trained on the same task that he or she is expected to perform in the context of daily activities, and training is specific to that situation. Generalization to other related situations is not expected as a consequence of the initial training. Thus the necessity of training a wide range and number of specialized, context-specific skills and routines is characteristic of the functional model.

## Metacognitive Remediation

Metacognition refers to the subjective knowledge and experience of one's own cognitive processes, which can be used to guide cognitive activity (13). Metacognitive training therefore places its major emphasis on increasing awareness of deficits, self-monitoring of errors, and self-regulation in order to improve the ability to independently recognize or anticipate the need for compensatory strategies and utilize those strategies in the appropriate situations. Shallice's (14) neuropsychological model distinguishes between the cognitive levels of *processing structures* and two levels of *cognitive control*. Processing structures consist of special-purpose cognitive subsystems such as object recognition, semantic comprehension, spatial orientation, and so on, that can be analyzed by fractionation of the subsystems into the involved components. These cognitive sub-systems can also be organized into relatively invariant functional routines, or schema, such as eating breakfast or driving home from work. *Routine* control of activity is accomplished through relatively automatic and rapid selection of habitual schemata and the inhibition of weaker competing schemata. However, an additional level of voluntary, strategic, and *nonroutine* control is required when planning is required, when the correction of unexpected errors is required, when the required response is novel or not well learned, or when habitual responses need to be inhibited.

Reliance on the underlying assumption that patients will be able to develop sufficient awareness and insight to apply strategies in a variety of situations is a distinctive aspect of the metacognitive approach. Crosson et al. (15) has distinguished between intellectual, emergent, and anticipatory levels of awareness after brain injury. Different degrees of compensation may be available to patients, depending on their degree of awareness deficit. For example, patients with marked deficits of intellectual awareness may require external, task-specific compensation whereas patients with minimal awareness deficits may compensate by recognition or anticipation of problems while moving from one environment to another several times in the course of their daily functioning.

## REMEDICATION OF ATTENTION DEFICITS

### Remediation of Attention Deficits

Various components of attention have been identified and related to different cerebral networks. Posner and Rothbart (16) identified three different attention networks. The posterior attention network involves the parietal cortex, pulvinar and reticular thalamic nuclei and superior colliculus and is involved in orienting to and locating sensory stimuli in space. The anterior attention network involves the anterior cingulate gyrus and supplementary motor

area and appears active in the detection and selection of target stimuli and inhibition of responses to irrelevant stimuli. Although selectivity may occur on an automatic or unconscious level, situations which are novel or complex will require conscious and strategic control over attention. The vigilance network involves the locus coeruleus and brainstem reticular connections with cerebral cortex, especially lateral frontal cortex. This system may be responsible for maintaining alertness and vigilance. Whyte (17) also reviewed evidence suggesting that attention was not a single cognitive process controlled by a focal brain region and indicated that the neural control of attention was mediated by various structures including the brain stem, subcortical structures, and cerebral cortex, which interact in a richly interconnected network. Whyte (17) suggested that the distribution of attention across this dense neural network had two important clinical implications. First, he suggested that different brain lesions could produce qualitatively different attention deficits due to disruption of distinct aspects of the attentional network. Second, lesions to different brain regions could produce similar attentional impairments due to the distributed and integrative nature of the attentional system. The effectiveness of remedial interventions would, in principle, depend upon providing treatment directed at the precise nature of the attentional deficit.

Impairments of attention are common after TBI, and include reductions of processing speed, difficulty sustaining the focus of attention (e.g., maintaining concentration or a train of thought), and limitations in the ability to regulate the allocation of attention in complex situations (e.g., shifting attention to multiple speakers, or between several ongoing tasks). Therefore it is not surprising that some of the earliest formal attempts at cognitive remediation after TBI were directed at deficits of attention. In an early study of attention process training (APT), Sohlberg and Mateer (18) provided the training to four patients and compared it with training for visual perceptual abilities, using a multiple baseline across subjects design. The patients were all at least one year, and up to 6 years, after injury, so it is likely that their deficits were stable. All four subjects demonstrated gains on a single attentional-outcome measure following APT, but not after the visual-perceptual treatment. The measure used to assess improvements in attention was similar in several respects to the training tasks, so it is likely that the improvements reflected some degree of familiarity and practice with the task demands and near transfer to the outcome measure.

A more recent study of APT (19) used a randomized crossover design to compare APT with a "placebo" condition that consisted of education and support. The 14 patients with acquired brain injury were again all at least one year post-injury, ranging as far as 22 years post-injury. Most of the patients had sustained severe TBI,



including positive neuroimaging, and they all exhibited impairments of attention on neuropsychological evaluation and subjective report by the participant and/or a significant other. The APT tasks were again administered in accordance with a hierarchical approach, although the training exercises were selected for each of the patients based on their specific profiles of attention deficits. Treatment effects in this study were evaluated on a range of outcome measures, including neuropsychological measures intended to reflect specific components of attention, standardized questionnaires, and structured interviews. Significant benefits of APT, compared with therapeutic support, were most apparent in patients' self-reported changes in attention and memory functioning. Improvements in cognitive functioning on neuropsychological measures intended to assess the anterior attentional network for the regulation of attention (but not measures of spatial orienting or vigilance) were also greater following APT, and paralleled the patients' self-reports of improved functioning. The specificity of improvements on an aspect of attention related to the regulation of attention, and relationship of these improvements to patients' subjective improvements in their daily functioning, argues against the interpretation that the benefits of treatment were due either to generalized stimulation or task-specific practice effects. These findings also suggest that the benefits of training are due to patients' improved ability to control their attention, rather than restoration of more basic attentional processes.

Several additional prospective, randomized, controlled studies are consistent with the view that treatment for attention deficits are effective during the postacute phase of recovery from TBI, and related primarily to patients' ability to understand the nature of their deficits and use appropriate compensations in functional situations. One study (20) treated 26 people who had sustained a TBI between one and six years earlier and were living in the community. The attention treatment consisted of computer-based tasks directed at improving participants' ability to focus their attention or allocate their attention between tasks; in addition to practice on the computer-based tasks a significant portion of each treatment session was devoted to providing participants with feedback about their performance and implementing strategies to compensate for their attention difficulties. The group receiving the attention treatment improved significantly over the course of treatment, although these effects were relatively weak and did not transfer to additional measures. In another study (21) attention remediation was compared with a "placebo" condition of recreational computing. The patients varied widely in their time post injury and severity of deficits, and included etiologies of both TBI and stroke, although neither of the latter two factors was related to the effects of treatment. Training was intended to address attention control processes such as manipulating information in

working memory or dividing attention between two tasks, and was compared with the effects of recreational computing. Some benefit of the attention treatment were apparent immediately after treatment, but were more evident six months after treatment, at which time the patients who received the attention treatment showed continued improvement while the patients who used recreational computing did not improve, and in some cases their performance deteriorated. The treatment group's pattern of modest initial improvement followed by increased benefits over time may have represented their increased proficiency in the use of strategies in their daily functioning. This pattern of prolonged benefits of treatment being related to the active use of strategies, and lack of benefits when strategies are no longer used, is evident in a number of studies and consistent with the view that improvements in functioning are related to patients' ability to learn and implement compensatory strategies in their everyday functioning.

This approach also served as the basis for an intervention that was intended specifically to teach patients with TBI to compensate for the experience of "information overload" due to their slowed information processing during the performance of daily tasks (22). Twenty-two patients with TBI, most of whom were more than six months post-injury, received either "Time Pressure Management" training or generic instructions to improve their concentration. The Time Pressure Management (TPM) was intended to increase patients' awareness of errors and use of strategies to manage demands under distracting conditions that were likely to be encountered in their everyday lives. Participants receiving TPM showed significantly greater use of self-management strategies during task performance, particularly on more complex tasks that allowed them to adjust their approach to the task, but not on basic reaction time tasks in which such a strategy could not be applied.

Patients with mild TBI often complain of difficulties with the more complex aspects of attention, and are likely to exhibit selective impairments of attention functioning in the context of generally intact cognitive functioning. One small, observational study (23) has evaluated the effectiveness of an intervention intended to improve "working attention" in four patients with mild TBI, compared with four patients who did not receive treatment. The intervention emphasized the use of strategies to allocate attention resources and manage the rate of information during task performance. The patients receiving attention treatment demonstrated "clinically significant gains" on objective measures of attention and significant reductions of self-reported attentional difficulties in their daily functioning.

Overall, these studies suggest that significant benefits can be obtained by patients with attentional difficulties during the postacute period of recovery from TBI.

Gains on objective measures of attention are related to subjective improvements in patients' everyday functioning. Finally, these benefits appear to be related to patients' abilities to apply compensatory strategies in their daily functioning, even for relatively basic deficits such as reduced processing speed, rather than by restoration of the underlying attention processes. The evidence for generalized, functional improvements in attention functioning after treatment in the above cited studies rests primarily on patients' subjective report. However, one single-subject study has reported beneficial effects of an intervention intended to facilitate control over attention during functional activities, such as decreasing the frequency of lapses in attention while the patient was reading novels and texts (24).

The benefits of remediation for attention deficits during the acute period of rehabilitation for TBI are not readily apparent, and it does not appear possible to distinguish the effects of specific attentional training (such as APT) from the more general effects of acute brain injury rehabilitation (25) or spontaneous recovery (26).

### REMEDICATION OF MEMORY DEFICITS

Memory complaints are ubiquitous after brain injury. However, the memory difficulties seen after TBI typically do not reflect a classic amnesic disorder. Instead, memory difficulties are likely to be due to a number of different factors, and are unlikely to represent a unitary deficit. For example, attention deficits such as distractibility or slowed processing are commonly believed to cause impairments in the acquisition of information, and executive impairments may cause memory failures due to the failure to adequately organize material or initiate efficient memory retrieval processes (27).

One of the first descriptions of remediation for memory deficits after brain injury (28) presented two case studies on the use of semantic elaboration and visual imagery techniques to improve the encoding of information. After the effectiveness of these techniques was demonstrated in the laboratory, they were applied to the patient's presenting problem of reduced academic performance. The success of treatment was assessed by the patient's improved subjective ratings of her memory functioning and reduction of negative self-statements, and her ability to remain in her academic classes with less subjective difficulty. Review of her academic performance suggested that she was able to apply the procedure in her everyday life, although the effects were not as great as were seen in the laboratory situation.

Ryan and Ruff (29) examined the general effectiveness of compensatory memory remediation by combining a number of strategies for improving verbal and non-verbal memory capacities in a comprehensive remediation

program. Treatment was provided to ten patients with TBI who exhibited persistent mild to moderate memory deficits. Interventions included instruction and practice in the use of rehearsal, elaborative semantic encoding and associative strategies, imagery construction, "personalized emotional techniques", external memory strategies, and group education and practice with the various memory compensations. Individualized cuing procedures were developed for each patient and practiced on a daily basis. Control patients participated in recreational activities and psychosocial support. At the completion of the treatment both groups demonstrated significant improvement on memory measures, without any apparent specific benefits from the specialized memory remediation program. Subsequent analysis did suggest that the patients with relatively milder cognitive deficits showed greater benefit from the memory remediation strategies, while those with moderate residual impairments did not benefit from treatment. This study is important for several reasons. First, the treatment more closely resembled a multidimensional, clinical protocol than in many experimental studies. Second, the study evaluated the differential effectiveness of treatment in relation to the severity of cognitive impairment. Finally, the study provided an explicit comparison between active, specialized memory remediation and a nonspecific intervention.

Kaschel and colleagues (30) conducted a prospective, controlled study of a visual imagery technique for the rehabilitation of participants with mild memory impairment after acquired brain injury. The intervention consisted of a standardized imagery-acquisition procedure to promote imagery-generation, overlearning and automatization, and included an individually-tailored training period directed at the transfer of the strategy to everyday relevant materials. Visual imagery was compared with "pragmatic memory training" that included practical guidelines to improve memory and the use of notebooks and calendars. Twenty-four patients with TBI had initially been referred for memory rehabilitation, and memory problems were considered to be of primary importance, although patients with severe memory impairment were excluded. Significant improvement was apparent only for the imagery condition on the recall of verbal material, consistent with the expected effects of treatment. The improvements associated with visual imagery training were paralleled by positive changes in relatives' ratings of patients' memory functioning and were maintained at three month follow-up.

Another randomized controlled trial (31) has specifically compared "repetitive drill and practice" on memory tasks with training in cognitive strategies to improve memory functioning after TBI. Cognitive strategies to improve memory functioning were explained, demonstrated, and practiced three times a week for six weeks, and patients received daily homework stressing the

importance of application of memory strategies in everyday life. Intervention was highly individualized, with the specific memory problems selected for training based on the subjects' report of difficulties experienced in their daily functioning. Patients in both the strategy training and "drill and practice" groups reported subjective improvements in memory functioning, but significant effects on objective memory performance could only be demonstrated in the strategy training group, and this difference was maintained at 4 month follow-up.

In a follow-up study four years after the initial training (32), subjective memory and objective memory performance were the same for both patient groups and equivalent to a no-treatment brain injury control group (and still well below the level of normal control subjects). Of note, several subjects in the strategy training group showed a decline in their performance, while the "pseudotreatment" group showed continued, significant improvements despite the fact that patients were between five and 25 years post injury at the time of follow-up. In contrast with this study, Wilson (33) evaluated 26 patients with traumatic head injury who had been referred for memory therapy five to 10 years earlier. On standardized memory testing, most patients remained stable and 8 patients showed improved performance. It was noted that many subjects were using more memory aids and strategies at the time of follow-up assessment than they were at the completion of their initial memory rehabilitation, which may have accounted for the positive findings (34).

*Prospective Memory* The ability to remember to do something at some future time, referred to as prospective memory, appears to be one of the most common memory problems for patients with acquired brain injury (35). Prospective memory interventions may be based on modifications of other memory interventions, such as space-retrieval and distributed practice techniques or use of elaborative encoding strategies. A series of case studies (36, 37) described a specific prospective memory training procedure in five patients with severe traumatic brain injury. Training consisted of giving the patients simple, repetitive, one-step prospective memory tasks to be carried out at increasingly longer time intervals following instructions, ranging from two to ten minutes. The patients all improved with practice on the prospective memory tasks, with some evidence of improvement on neuropsychological measures and observations of daily memory functioning. However, the limited time between the assignment of tasks and their execution, lack of intervening or complex tasks, and degree of therapist control all limit the relevance of the training to real life demands.

*External Memory Compensations* Patients with memory impairments after TBI are commonly taught to use a

memory notebook or diary to compensate for their difficulties in spontaneous, or unassisted, recall of information. One randomized controlled trial (38) has compared notebook training with supportive therapy for eight patients with TBI, all more than two years post injury. The treatment consisted of teaching a specific protocol for use of a memory notebook, and individualized modifications to address the subjects' personal needs and application to novel settings. Patients who received the notebook training reported fewer observed, everyday memory failures than the supportive therapy subjects. Three of the subjects who received the memory remediation were still actively using the memory notebook to assist with their daily activities at six month follow-up.

In this study, and in the studies described above using some form of strategy training, the patients who benefited from treatment all exhibited relatively mild memory difficulties. In contrast, patients with severe memory deficits after TBI appear more likely to require training in the use of specific compensations that can be applied to specific tasks, rather than attempts to remediate their underlying memory deficits through the use of strategies. For example, the use of a memory notebook has been shown to be superior to verbal rehearsal strategies when patients are required to remember specific information, particularly for patients with more severe memory impairments (39). While external memory compensations such as memory notebooks are commonly employed in cognitive rehabilitation, patients with severe memory difficulties are likely to require an extended period of training to ensure the practical application of a memory notebook (40, 41).

*External Cuing and Environmental Compensations* In the last several years there has been increased development of external cuing and assistive technologies as a compensation for memory impairments after TBI. For example, three studies have described the use and effectiveness of a portable voice organizer to help patients to recall their therapy goals (42) or to prospectively remember to perform relevant everyday tasks (43, 44). The use of existing technologies to assist people with memory deficits will typically require additional training, and consideration of multiple factors that influence the selection of an external cuing system (e.g., the patient's cognitive strengths and weaknesses, knowledge and familiarity with specific technologies, and the necessary resources and "user friendliness" to support programming and maintenance of the assistive device (45, 46).

Several assistive devices have been developed specifically with the intent of improving the cognitive functioning of people with acquired neurocognitive impairments, such as the Essential Steps cognitive orthotic system (47), the ISAAC cognitive prosthetic system (48) and the NeuroPage paging service (49–51). Initial evidence for the

effectiveness of these systems is limited to descriptive case studies (47–49). More recently, Wilson and her colleagues (50) have evaluated the effectiveness of the NeuroPage portable paging system to reduce everyday memory failures during the performance of functional activities, such as remembering to take one's medication or shut off appliances. A randomized controlled trial of the paging system was conducted for patients with persisting memory difficulties, many of whom had been referred only after previous interventions had failed. For each patient, the use of the pager was adapted to address specific problems in their typical daily functioning (e.g., keeping appointments) identified by the patient or a relative. Significant improvements in the ability of participants to carry out everyday tasks with the use of the pager were apparent, compared with no-treatment and baseline conditions. The paging system was noted to be most useful for those people who needed to carry out certain tasks on a regular basis and had some insight into their memory deficits. Based on this research, a commercial service offering NeuroPage was subsequently established through the National Health Service in the United Kingdom (51). Among the first 40 patients, with diverse etiologies of memory dysfunction, who were recruited into this study, 31 were reportedly able to use the pager successfully. The most frequent types of reminders were related to taking medication, daily orientation (e.g., getting up in the morning) and daily household activities (e.g., making lunch, taking a shower, doing the laundry) and these accounted for about 75% of messages provided by the pager. Among the patients who used the paging system consistently for some time, the authors noted several patterns of use. One group of patients continued to use the pager on a consistent basis for many months with no appreciable change in the messages required each week. Another group of patients continued to use the pager, but adjusted the number of messages they required. Some clients found that they were able to discontinue use of the pager after some time, suggesting that the pager served to establish their routine and they could then manage alone or use a different type of self-directed reminder. It is unclear whether these different patterns of use correspond to different patient characteristics (e.g., severity of memory impairment, presence of neurocognitive co-morbidities, level of motivation) although this might provide important clinical information in the future. It is clear that different forms of memory compensations are best selected only after careful consideration of these, and other, patient characteristics.

### REMEDIATION FOR DEFICITS IN EXECUTIVE FUNCTIONING

Disturbances in executive functioning are prevalent after acquired brain injury, and represent significant obstacles

to social functioning, work and rehabilitation. Disorders of executive functioning may affect the ability to anticipate the effects of our actions, appreciate alternative perspectives, and to recognize other people's reactions to our behavior and modify our actions accordingly. Disturbances of executive functioning may be apparent after various types of cortical or subcortical damage, but are often associated with damage to the frontal lobes. The dorsolateral frontal cortex has extensive connections with polysensory posterior association areas (52) and appears to be related to deficits in complex discrimination and association (53). The medial prefrontal cortex has been implicated in the processes of motor initiation and motor regulation and also appears to play a role in tasks requiring complex attention and planning (52). The orbitofrontal cortex is part of paralimbic cortex (5) has been related to disturbances of complex social and emotional behavior in humans (54, 55).

Patients with frontal-lobe damage may exhibit dissociation between the relative preservation of verbal knowledge, and the failure of this knowledge to guide behavior in pursuit of the appropriate goals and actions. This tendency to disregard the requirements of a given task, even when these are verbally appreciated, represented a fundamental aspect of executive dysfunction, referred to as *goal neglect* (56). Levine and his colleagues (57) developed a formalized intervention for executive dysfunction, referred to as goal management training (GMT), based on the theory of goal neglect. The process of GMT involves five discrete stages of what is essentially a general purpose, problem-solving algorithm starting with an evaluation of the relevant goals in a situation, through the selection of sub-goals, and then monitoring the results of one's attempts at a solution; in the event of a mismatch the entire process is repeated. Thirty patients with mild to severe TBI were randomly assigned to receive either GMT or an alternative treatment of motor skills training. GMT consisted of a single session in which participants were instructed to apply the problem solving algorithm to two functional tasks. Patients in the motor skills training condition practiced reading and tracing mirror-reversed text and designs. Treatment effectiveness was assessed on several paper and pencil tasks which resembled the training tasks, and were intended to simulate the kind of unstructured everyday situations which might elicit goal management deficits. Participants who received GMT demonstrated significant reduction in errors and prolonged time to task completion (presumably reflecting increased care and attention to the tasks) on two of the three outcome measures following the intervention. The entire treatment in this study consisted of one hour of intervention, which may be adequate to suggest the potential efficacy of GMT but provides little evidence of its clinical effectiveness.

Another prospective randomized controlled study (58) utilized a problem solving intervention intended to facilitate patients' ability to reduce the complexity of a multistage problem by breaking it down into manageable subgoals. Training was provided 37 patients who were identified as poor problem solvers on formal tests of planning and response regulation. Twenty participants received an intervention directed at remediation of executive function deficits, while 17 participants received an alternative intervention consisting of memory retraining. Patients who received the problem solving training demonstrated significant gains on neuropsychological measures of planning ability as well as improvement on behavioral ratings of executive dysfunction, such as awareness of cognitive deficits, goal-directed ideas, and problem-solving ability.

Rath and his colleagues (59) evaluated the effectiveness of an "innovative" treatment for problems-solving deficits, compared with a "conventional" neuropsychological group treatment for patients with TBI. The patients were described as being "higher functioning" but with documented, persistent impairments in social and vocational functioning (e.g., job loss, marital difficulties), an average of 4 years post-injury. The conventional treatment consisted of group exercises intended to improve cognitive skills and provide support for coping with emotional reactions and changes after injury. The innovative problem-solving intervention focused on the development of emotional self-regulation strategies as the basis for maintaining an effective problem-orientation, along with a "clear thinking" component that included training in problem solving skills using role-plays of real-life examples of problem situations. Both groups showed significant improvement of their memory functioning after treatment. Only the problem solving group treatment resulted in significant beneficial effects on measures of executive functioning, self-appraisal of "clear thinking", self-appraisal of emotional self-regulation, and objective observer-ratings of interpersonal problem solving behaviors in naturalistic simulations.

These three randomized controlled studies demonstrate that training patients with TBI to use formal problem-solving methods can be an effective intervention. The study by Rath et al. (59) suggests that the development of strategies to improve emotional self-regulation may be particularly relevant to the clinical treatment of patients with executive functioning deficits after TBI, and provides the clearest evidence that this intervention may improve patients' performance in everyday situations.

Several studies have attempted to remediate executive function impairments through the development and internalization of strategies for effective self-regulation. According to Luria (60), self-regulation is achieved through the covert, verbal mediation ("inner speech") of purposeful activity. However, simply having the patient repeat the task

instruction is insufficient to re-establish self-regulation (61). Cicerone and Wood (62) used a self-instructional training procedure to encourage planning and self-monitoring, while inhibiting inappropriate behaviors. The training procedure included three stages of self-verbalization, progressing from overt verbalization, through faded verbal self-instruction, to covert verbal mediation of appropriate responses. Over the course of training, there was a dramatic reduction in task-related errors as well as more gradual reduction and eventual cessation of off-task behaviors. Generalization to his functional, real-life behaviors were observed only with additional instruction and practice in the application and self-monitoring of the verbal mediation strategy to his everyday behaviors. A subsequent study (63) replicated this finding with six patients who exhibited impaired planning and self-monitoring after frontal lobe injury. Five of the six patients showed marked reduction of task-related errors and perseverative responses, suggesting that the effectiveness of training was related to the patients' improved ability to inhibit inappropriate responses. Self-instructional training has also been shown to be an effective component of interventions directed at attention (22, 64) or memory (65).

There is a potential paradox in attempts to remediate disorders of executive functioning, in that these disorders effect the processes of self-monitoring and self-regulation that are an inherent aspect of remedial compensations. Successful compensation appears to require some residual capacity to deliberately and consciously apply strategies. A recent, uncontrolled group study (66) of patients with documented frontal lobe damage, severe cognitive impairments and poor self-awareness has demonstrated improvements after four months of treatment in patients' knowledge and use of self-regulatory strategies, and the self-rated effectiveness of strategies in their daily functioning. Several case studies have also described interventions that improved the patients' ability to self-monitor their behavior (67, 68). In each of these studies, the goal of cognitive remediation was not the training of task-specific performance, but the training and internalization of regulatory cognitive processes. In contrast, limited success was observed in two descriptive case studies of patients with orbitofrontal damage that resulted in social cognition and affective regulation. In both cases, the patients were able to improve specific behaviors in the situations in which they had been trained, but could not effectively modify their problematic social and emotional responses in novel, real-life situations, despite extensive treatment (69, 70).

### **Remediation of Pragmatic Communication Deficits**

Deficits in executive functioning may be expressed as a disturbance of the social and affective and pragmatic aspects

of communication, as noted by Eslinger in this volume. Thus, while classic neurologic syndromes of language impairment are not commonly seen after TBI, patients with TBI frequently exhibit impairments of pragmatic communication. These may include the loss of coherence and cohesiveness during narrative discourse, difficulty interpreting subtle, contextual aspects of communication (e.g., humor, sarcasm, irony), and failure to interpret or respond to non-verbal cues in the context of social communications. Helffenstein and Wechsler (71) evaluated the effectiveness of a group intervention designed to improve interpersonal communication skills, in which the central aspect of treatment was to provide patients with systematic review and feedback concerning their interpersonal, communication interactions. Beneficial effects were noted following this procedure, compared with a sample of subjects with TBI who received equivalent treatment contact without the systematic feedback. Specific improvements were noted on self-report measures of self-concept, ratings of interpersonal and communications skills, and the effectiveness of interpersonal communication in non-therapy, social settings. Several uncontrolled group studies (72, 73) and single-case studies (74, 75) have reported improved pragmatics and conversational skills following treatment that included systematic feedback and self-monitoring of interpersonal communications. The focus of the group-based treatment was to improve patients' communication competence in social contexts, including initiation, topic maintenance, turn taking, and active listening. Within each of these skill areas, treatment addressed the subjects' awareness of obstacles to effective communication, practice of effective communication, and generalization to natural contexts. The goal of the generalization phase was to apply the trained skills to relevant activities and settings in each individual's particular community, incorporating practice with parents and peers (72). One case study (76) has indicated that improvements in narrative discourse that were seen in treatment did not transfer to the patients' functional conversations. This lack of generalization was attributed to the "acontextual" nature of the treatment, and can be contrasted with the treatments that included specific interventions to promote the generalization of communications skills to the patients' real-life contexts and activities.

### INTENSIVE-HOLISTIC COGNITIVE REHABILITATION

Cognitive rehabilitation of TBI may best be achieved through a comprehensive, *holistic* approach to the treatment of cognitive, emotional, and functional impairments and disability. Comprehensive-holistic neuropsychological rehabilitation is centered around the goals of fostering patients' awareness of their functional potential and

adapting to the chronic limitations imposed by their injury, in order to alleviate disability in everyday, social functioning. Ben-Yishay was perhaps the first clinician to delineate and advocate the need for a holistic approach to the neuropsychological rehabilitation of individuals with brain injury (77). In discussing the rationale for the holistic, or therapeutic milieu, approach to neuropsychological rehabilitation, Ben-Yishay and Gold (78) emphasized that the neurobehavioral manifestations after traumatic brain injury are dynamic and multidetermined. They suggest that "it is meaningless to make rigid distinctions between higher and lower level cognitive functions or between physiogenic and psychogenic factors in emotional disturbances" after brain injury (p. 194). Thus, neither isolated cognitive remedial exercises to improve attention, memory, and or other "fragmentary" deficits, nor a focus exclusively on traditional psychotherapeutic interventions, are likely to be effective. Instead, an effective rehabilitation program must systematically integrate interventions directed at the remediation of cognitive deficits, functional skills, and interpersonal functions. Improvements in functioning are typically accomplished by an improvement in the effective functional application of residual cognitive abilities, rather than restoration of the underlying cognitive deficits, per se.

An early study of the relationship between holistic cognitive rehabilitation and employability (79) evaluated the effectiveness of a clinical program consisting of three phases. The first phase consisted of individual modules of cognitive remediation and group treatments to improve interpersonal communication, social competence, and awareness and acceptance of the consequences of brain injury. Treatment was provided within the model of a "therapeutic community" which included the engagement of family members and significant others in the treatment process. The second phase of treatment was devoted to structured work trials, and the third stage involved actual work placements. Employability ratings suggested that 84% of the previously unemployed patients were able to engage in some form of productive activity following the neuropsychological rehabilitation program. A subsequent study (80) suggested that patient characteristics related to motivation, affective regulation, and accurate self-appraisal were more closely related to effective functioning after treatment than neurologic or neuropsychological characteristics.

The relative contributions of individualized cognitive remedial interventions and small-group based exercises in interpersonal communication within the context of a holistic neuropsychological rehabilitation program have been explicitly evaluated (81). One group of patients received a mixture of cognitive and interpersonal interventions. A second group of patients received the individualized cognitive remedial interventions but did not receive interpersonal communication training. The third group received

the initial, basic attentional training followed by the interpersonal remediation, while the individualized cognitive interventions were withheld. Only the two groups receiving the individualized cognitive remediation showed improvement on near transfer measures of cognitive functioning, which may have reflected practice effects as these measures were similar to the tasks used in treatment. There was a tendency for patients receiving the interpersonal training to show improvement on measures of affect regulation, self appraisal and self esteem. These findings are consistent with the holistic approach to treatment, indicating that the greatest gains in functioning may be achieved through the integrated treatment of both cognitive and interpersonal functioning.

There have been two prospective, randomized controlled studies of comprehensive rehabilitation for patients with TBI. Both studies are best considered as efficacy studies, in that treatment was provided to selected patients in a highly constrained environment. The first of these studies (82) compared the effects of structured cognitive rehabilitation with treatment providing professional attention and psychosocial support. Participants with moderate-to-severe TBI, one to seven years post-injury, were recruited from the community and “quasi-randomly” assigned to treatment conditions. Potential participants with expressive or receptive language disturbance, significant visual deficits, prior neuropsychiatric disturbance, or poor motivation were excluded from treatment. Subjects in the neuropsychological treatment condition received specific treatments directed at improving attention, memory, visuospatial ability, and problem solving. Subjects in the alternative, psychosocial treatment condition received an equivalent amount of treatment directed at coping skills, interpersonal functioning, and personal development. Both groups improved, but there was little overall difference between the two groups on measures of neuropsychological functioning or emotional adjustment. The findings suggest that non-specific factors (e.g., establishment of a therapeutic alliance and expectations for improvement) contributed to the effects of treatment in both conditions.

Salazar and colleagues (83) evaluated the efficacy of cognitive rehabilitation for 120 people with moderate to severe TBI (an average of 38 days post injury) within a single, military medical referral center. The program was based on the principles of a “therapeutic milieu” modified to meet the needs of patients returning to active military duty. Patients were randomly assigned to receive either a multidisciplinary, in-hospital cognitive rehabilitation program or home-based education and encouragement from a psychiatric nurse. There was no difference between groups on either return to work or fitness for military duty one year after treatment. The groups also did not differ on measures of neuropsychological

functioning, although participants with more severe injuries demonstrated greater improvement after the cognitive rehabilitation program.

In both of these studies, the ability to generalize the results to the typical clinical situation is limited. Length of treatment was relatively brief (eight weeks) in both studies, and significant subject selection biases were apparent. Salazar (83) noted the “extraordinarily high return-to-work rates” and suggested that participants’ high pre-injury education and level of functioning, significant degree of spontaneous recovery, and ready availability of (military) employment after injury might have limited the ability to detect any differential benefits from the cognitive rehabilitation program.

Clinical studies of comprehensive-holistic cognitive rehabilitation have generally reported more positive results. One prospective, non-randomized study evaluated the benefits of either a “standard” program of postacute neurorehabilitation or a more structured and intensive milieu-based rehabilitation program (84). Treatment was provided to 56 patients with primarily moderate-to-severe TBI who had been referred for cognitive rehabilitation, either from acute rehabilitation or from the community. All patients were screened and assigned to one of the treatment programs based on clinician’s judgments regarding the most appropriate treatment. As a result of this selection process, patients who received the more intensive-holistic cognitive rehabilitation program were further post-injury, more likely to exhibit impaired self-awareness, and exhibited lower initial levels of community functioning on admission to rehabilitation. Overall, patients in both treatment conditions showed significant improvements in community integration; the patients who received the intensive-holistic treatment program showed greater improvement despite the fact that they were less functional and further post-injury at the time of admission. Improvements in overall neuropsychological functioning were associated with clinically significant improvement in community integration. Patients’ satisfaction with their cognitive functioning after treatment was also a strong indication of successful community integration, again suggesting the contribution of psychological factors in patients’ ability to benefit from cognitive rehabilitation.

A number of retrospective studies have also reported positive benefits from comprehensive neuropsychological rehabilitation programs, compared with patients who did not receive rehabilitation (85–87). Observational studies in this area have also demonstrated significant improvements in community functioning after treatment (88–90) that persist for many years (91, 92). These clinical studies support the effectiveness of a programmatic approach to cognitive rehabilitation for people with TBI, including those who have been unable to resume effective functioning several years after injury.

## CONCLUSIONS

Cognitive rehabilitation is an integral part of the neurorehabilitation of TBI. The first published case studies on remediating memory deficits in brain damaged individuals appeared in 1977 (28). The clinical practice of cognitive rehabilitation has matured substantially in the ensuing 25 years. Empirical evidence for the effectiveness of cognitive rehabilitation is beginning to catch up with clinical practice. Recent systematic reviews of the literature (3, 93) have identified 20 randomized, controlled trials addressing the remediation of higher cognitive deficits in patients with TBI, with 35% of these published within the last 5 years. In clinical practice, there is general consensus that cognitive rehabilitation (regardless of the specific approach taken) should be directed at improving patients' everyday functioning and quality of life. Most studies of interventions for specific cognitive functions have been limited to assessing the effectiveness of treatment at the impairment level, although several recent studies have demonstrated clinically meaningful improvements in community integration following comprehensive-holistic cognitive rehabilitation.

Efforts to provide patients with the best available treatment, and to evaluate the effectiveness of cognitive rehabilitation, need to consider the complex nature of the interventions, the heterogeneity of patients with TBI, and the need to individualize treatment according to the unique and varied demands of patients' lives. For these reasons, the practice of cognitive rehabilitation will continue to rely upon clinical judgment and experience. Cognitive rehabilitation is not a distinct form of service, or the purview of any single discipline, but a specialized form of rehabilitation that requires adequate professional training in the nature of brain-behavior relationships, the neurologic basis of intact and impaired cognitive function, and the rehabilitation of cognitive disorders (94). It is also essential for clinicians who practice cognitive rehabilitation to maintain their knowledge of the literature and the empirical basis for the effectiveness of interventions as a means of guiding treatment selection and implementation. The increasing emphasis on evidence-based (cognitive) rehabilitation is not intended to supplant clinical judgment, but to inform it through the best available scientific evidence.

The ability to secure adequate reimbursement for cognitive rehabilitation remains a challenge in many cases, sometimes due to the position taken by referral sources and payers that cognitive rehabilitation remains an "investigational" procedure. The increasing evidence for the effectiveness of cognitive rehabilitation, and familiarity with evidence-based recommendations for cognitive rehabilitation by practicing clinicians, should help to facilitate this process. There is already evidence that some major insurance providers are incorporating the current evidence for effectiveness of cognitive rehabilitation in their clinical

policy bulletins. In other cases, clinicians who are providing treatment in accordance with evidence-based recommendations may be able to obtain approval for cognitive rehabilitation through the external claim review process that is available in many states.

From a scientific perspective, the evaluation of the effectiveness of cognitive rehabilitation is, of course, a continuous and ongoing process. There continues to be some debate regarding the most appropriate methodology for conducting research on cognitive rehabilitation. Well-designed single-case studies can provide important information, especially regarding novel or innovative interventions. Highly controlled, clinical trials remain the most sure way to subject an intervention to rigorous confirmation of its efficacy. The selection of an appropriate research methodology will depend on multiple considerations, including the state of the already existing evidence, the ability to standardize the intervention across subjects or settings, and the availability of resources required to conduct the study. Perhaps the most compelling need in this area is the establishment of sustained programs of research that develop and evaluate the effectiveness and utility of an intervention through increasingly rigorous and practical methods, including the replication of findings across settings. This has generally not been achieved in the field of cognitive rehabilitation, with some exceptions (18, 19, 49–51). There is also a need to assess the external validity of cognitive rehabilitation, particularly through the use of outcome measures that are congruent with the research intentions. For example, the use of functional imaging may provide information about the degree of functional plasticity and nature of cerebral reorganization (if any) associated with a specific intervention. However, it can not be assumed that changes in the pattern of cerebral activation, even when present, are related to improvements in the individual's neuropsychological performance or everyday functioning. This will require that these interventions be assessed with an appropriate range of relevant health-outcome measures (e.g., functional limitations, community integration, subjective well-being). It is only through a sustained program of research that cognitive rehabilitation will fulfill its clinical and scientific promise, to improve the quality of lives for people with neurocognitive disability.

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# 42

## Cognitive Impairments After TBI

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### INTRODUCTION

Traumatic brain injury (TBI) is associated with several types of pathophysiology that damage cerebral cortex and subcortical nuclear structures as well as white matter connections (see chapter by Povlishock and Bullock for more details). The resulting changes in brain anatomy and physiology disrupt the typical functioning of specific structures and the larger neural networks they comprise, leading to subsequent neurological and neurobehavioral impairments. In addition to these direct brain-behavior effects of TBI, there can be many complicating medical and psychological problems that contribute to post-traumatic cognitive, behavioral and emotional impairments. These are detailed in several chapters throughout the text and underscore the complex nature of TBI. Despite their prevalence, cognitive impairments must be carefully evaluated on an individual basis, as they may be influenced by pre-existing conditions (e.g., learning disabilities, attention deficit hyperactivity disorder, substance abuse, prior head trauma), co-morbid conditions (e.g., seizures, major depression, pain, and medication side-effects) and differences in TBI effects and recovery. As an example, recent study identified a significant effect of major depression in lowering cognitive test scores after TBI (1). Hence, a multidisciplinary and comprehensive approach to TBI is necessary for best treatment outcomes.

Attentional and memory problems after TBI are among the most common cognitive impairments reported

by patients, their family members and clinicians (2, 3). Recent study has also emphasized that prominent working memory impairments occur after TBI (4). Such cognitive deficits are frequently accompanied by a spectrum of other cognitive, social, emotional and behavioral changes as well. This chapter provides an overview of cognitive impairments that are commonly associated with TBI in adults. Accompanying chapters by Kreutzer (*Neuropsychological Assessment and Treatment*), Cicerone (*Cognitive Rehabilitation*), Murdoch (*Speech Disorders*), Wehamn (*Vocational Rehabilitation*), Coelho (Language and Communication), Arciniegas and Silver (*Cognitive Psychopharmacology*) and Johnston (*Functional Assessment and Outcome Evaluation*) address important inter-related aspects of cognition and TBI. The importance of these topics stem from the fact that the long-term effects of TBI on personal, social and occupational ability and disability can often be related to cognitive, behavioral and emotional functioning. Indeed, cognitive measures are among the most important predictors of patients' return to work and independent living, even among those with good medical recoveries (4–7).

### NEUROPSYCHOLOGICAL EVALUATION

Neuropsychological assessment encompasses clinical and psychometric testing procedures that survey and

objectively measure the effects of cerebral damage on cognitive, behavioral, social and emotional functioning (8, 9). These procedures typically employ a wide range of standardized cognitive tests and survey instruments, together with comprehensive interview and clinical assessment. Neuropsychological test scores can change in different ways depending upon TBI pathophysiology. To this end, a variety of specific assessment techniques have been developed to evaluate a patient's relative strengths and weaknesses in multiple neurobehavioral domains such as memory, language, attention, spatial cognition, executive functions, and social cognition. Scores are then interpreted in reference to available normative data that provide the typical range and variation in test performance. Interpretation of neuropsychological test scores is meant to identify the type and severity of cognitive impairments that in turn reflect general location and severity of brain injury. While some clinicians employ fixed neuropsychological batteries that administer the same compilation of tests to all patients, most clinicians use a flexible battery approach that focuses on specific problem areas identified through clinical exam and observation. The flexible battery approach also places a very strong emphasis on evaluating the patient's *pattern* of performance; that is, the possible causes for their impaired test score. For example, an impaired memory test score may be reflect attentional and encoding deficiencies, memory consolidation deficits, or poor retrieval of information. Delineating specific processing impairments may provide a more direct and efficient approach to remediation services that target impaired processes. Therefore, neuropsychological assessment, along with assessments provided through medical and diverse therapy services (i.e., physical, occupational, speech and recreational specialists) is geared toward identifying how best to intervene in the remediation of cognitive, behavioral, social and emotional impairments that are caused by TBI (see chapters by Cicerone and by Wehman for further discussion of this interface). The following sections cover specific cognitive processing domains that are particularly important in TBI.

### INFORMATION PROCESSING AND ATTENTION

Information processing measures are typically designed to determine the speed and accuracy of sensory-perception and perceptual-motor responses. These processes are mediated by diverse brain structures that include multiple cortical regions, subcortical nuclei and many white matter connections. The pathophysiology of head trauma may affect information processing in several ways. Sarno et al. (10) recently demonstrated that head trauma was associated with prolonged simple and choice reaction times to visual, auditory and tactile stimuli. Tactile stimuli

presented particular difficulty in comparison to vision and audition (i.e., sensory-specific deficit) as well as in combination with those modalities (i.e., cross-modal deficits). Mathias et al. (11) confirmed that reaction time speed was compromised after mild TBI, particularly as visual task difficulty increased and when inter-hemispheric transfer of information was required. The level of difficulty and transfer deficits were more evident for visual than tactile tasks in their study. Tinius (12) reported that similar to adults with attention deficit disorder, those with mild TBI were impaired on reaction time measures, underscoring the frequent finding of slowed reaction time after head trauma (13). However, reaction time changes interact with the particular type of tasks presented. For example, simple reaction time tasks are often completed in normal fashion after head trauma, but choice or complex reaction time tasks are frequently more difficult and lead to detectable impairments (14–16).

Zoccolotti and colleagues (17) sought to compare multiple information processing and attentional measures in a group of 106 patients with generally more severe TBI drawn from multiple European sites. The sample was tested at least 5 months after injury and 80% of participants suffered coma of 8 days or longer. Patients were presented with 4 computerized tasks with responses limited to button presses to measure accuracy and latency. The first 2 tasks were designed to require *intensive attention* and included measures of: (1) alertness (reaction time with and without a tonal warning) and (2) sustained attention (15 minutes of vigilant observation of horizontal bar movements). The final 2 tasks were considered measures of *selective attention* and hypothesized to be problematic for patients. These included: (3) selective attention (go no-go and design detection tasks) and (4) divided attention (simultaneous visual and auditory tasks, each to detect a specific pattern during continuous stimulus presentations). Patients showed considerably more difficulty in the selective attention tasks requiring go- no go responding (combining working memory with inhibitory control) or divided attention (increasing the working memory load), with up to one-half demonstrating deficits. Some difficulties were also evident in the more straightforward intensive attention conditions, varying between 9–33% of patients. However, coma severity had no statistically significant effects on the intensive attention measures of alertness and vigilance. Analyses also indicated considerable variability in performance amongst patients. This is not unexpected given the diverse trauma and personal characteristics of the sample. At least three subgroups were identified:

- A severely impaired subgroup, with a similar attention deficit profile as the overall sample (greater impairment in selective and divided attention tasks). This subgroup, comprising nearly 50% of the sample,

also had more severe trauma and longer length of coma. While all patients with mild and moderate levels of coma completed the divided attention task, 5% of severe and 26% of very severe coma patients were unable to complete the task.

- A less impaired subgroup with a large dissociation between normal alertness scores and poor divided attention scores. Nearly 44% of the sample showed this pattern of performance that argues against a nonspecific or generalized slowing of performance and supports the possibility of a specific divided attention deficit. We have encountered such deficits commonly in clinical practice, where they can be described as disorganized behavior, losing track of objects, paperwork and activities, and being able to undertake only one activity or task at a time.
- A third possible subgroup (comprising only 7% of the sample) included those with very long reaction times in both alertness and divided attention tasks, suggesting very slowed psychomotor speed.

The prolonged reaction times of TBI patients appear to be influenced by both the type of task and the working memory load that it requires, usually represented by the number of competing stimuli and choices. These cognitive deficits may be a behavioral index of diffuse cerebral damage that subsequently limits speed of information processing particularly as environmental demands increase, becoming either more concentrated or sustained over time. Hence, TBI patients must exert greater mental effort in cognitive and occupational tasks that may have been readily managed prior to injury. This can lead to increased physical and mental fatigue, even headaches, that may be mistaken for stress effects. In these cases, a reduced work load and schedule is usually recommended. In some TBI cases, the degree of attentional change is sufficient to warrant evaluation of attention deficit-type symptoms. This is typically undertaken with a combination of standardized tests of attention (such as the Working Memory Index from the Wechsler Adult Intelligence Scale and continuous performance tasks) and behavioral survey of attentional behaviors (such as the Brown Adult ADD Scale). Treatment of adult TBI patients with low dose stimulants can be of significant benefit to their occupational and daily functioning, particularly when combined with cognitive compensatory strategies.

### UNAWARENESS OF DEFICITS (ANOSOGNOSIA)

Anosognosia (meaning, literally, “without knowledge of disease,” a term introduced by Babinski (18)) is a common behavioral disorder occurring in neurological conditions, characterized by limited acknowledgment or

denial of neurological dysfunction. The symptoms of which the patient is unaware may vary, and include memory and cognitive deficits, hemiparesis, visual and other sensory disturbances, gait disorder and deficits of naturalistic action/limb apraxia (19, 20)

Patients’ inability to recognize functionally-relevant problems is known to be a major barrier to rehabilitation after closed-head injury (21). Disavowal of neurological impairment can take several forms, including lack of emotional concern for acknowledged deficits (anosodiaphoria), verbal denial of deficits that are implicitly acknowledged (e.g. patients claim that they can walk but never actually attempt to get out of bed), combined explicit and implicit denial of deficits, denial of ownership of an impaired body part (asomatagnosia or somatoparaphrenia), and, at the far end of the continuum, dislike or hatred of a dysfunctional body part (miso-plegia) (19, 22). Patients with this disorder can evidence dramatic abnormalities in behavior, such as throwing themselves from their beds “in order to get rid of that awful leg.” Although occurring in conjunction with other clinical syndromes such as spatial neglect, amnesia, and even thought disorders, dissociations of awareness of deficit from each of the associated clinical syndromes are reported, and thus anosognosia may be best characterized as an independent syndrome, at this time without a single neuroanatomic basis.

### Impact of Anosognosia

Although there are no formal studies of the possible contribution of anosognosia to a delay in seeking medical attention after closed head injury, numerous anecdotal reports suggest that unawareness of deficit (sometimes theorized to be partly due to a functional adaptation, e.g. “shock”) may keep patients from presenting promptly to a medical care provider or emergency room after head injury, especially if patients lack other bodily injuries. Currently, no treatments for closed head injury are available that depend critically upon initiation within a short period after an injury occurs, but in the administration of acute thrombolytic therapies after stroke it has been suggested that anosognosia is a barrier to treatment delivery (19).

The most relevant impact of anosognosia on rehabilitation after closed head injury is in patients’ acceptance of the rationale for participation in treatment (engagement in the rehabilitative program), and in their ability to participate in the program once having agreed to do so (19, 22, 23). It is reasoned that patients may put forward inadequate or inconsistent effort, preventing gains in strength and endurance. However, anosognosia and decreased motivation has not in formal studies been universally associated with a poorer rehabilitation outcome (24). The scope of rehabilitation for anosognosic patients may be more limited because of safety and supervision needs, and

fewer challenging tasks may be attempted in order to ensure that patients will not expose themselves to further harm or attempt to perform tasks of which they are incapable. Lastly, anosognosia presents a barrier to studying outcomes in head trauma rehabilitation. After traumatic brain injury, patients consistently report better cognitive, physical and emotional outcomes than do their loved ones and clinicians (25–29). This creates problems in interpretation of patient self-report data, which might under other circumstances be considered to be of greater validity than that of external observers (30).

### Mechanisms of Anosognosia

Proposals to account for unawareness of neurological deficits include: *psychological denial*, *modular dysfunction* at the level of an isolated cognitive or neurological subsystem or in a single semantic domain, *monitoring dysfunction* at a level of superordinate cognitive processing, and *multifactorial* theories postulating dysfunction in several cognitive domains (19, 22).

A detailed discussion of the putative mechanisms underlying anosognosia after brain injury is beyond the scope of this chapter. However, because of the importance of this theory, we will briefly discuss evidence regarding the mechanism of psychological denial. Weinstein and Kahn (31) first proposed that psychological denial may produce inability to acknowledge neurological deficits after stroke such as hemiparesis. Important clinical observations, however, are inconsistent with the psychological defense mechanism hypothesis. A coping strategy should be more utilized as recovery progresses, cognition improves, and chronic losses become apparent. Anosognosia is most apparent immediately post-injury, and gradually improves (19, 21, 22, 27, 30). A denial syndrome should be most severe for deficits posing the greatest potential ego threat, and less marked for deficits not likely to produce disability. However, modular dissociations in anosognosia not clearly based on subjective deficit severity (e.g. unawareness of visual problems but awareness of gait problems) are reported after head injury (22, 32). In subjects without brain injury, anosognosia can be induced by selective hemispheric anesthesia (19), but in the same individuals, this occurs more commonly after right- than left-sided injection. This asymmetry is difficult to explain on a psychological basis. Most critically, in brain-injured patients, it is unclear that anosognosia confers even temporary functional advantage, either in reducing subjective distress (33) or in improving function (34), which is central to the concept of a psychological defense. Schacter and Prigatano (35) wrote an excellent summary of the controversy about this issue:

Although most observers agree that defensive denial of a kind that can be observed in non-brain-damaged patients plays *some* role in the unawareness phenomena exhibited by *some* brain-damaged patients, the nature

and extent of the contribution is still the subject of debate . . . The critical problem . . . is to develop adequate criteria for distinguishing between defensive and nondefensive forms of unawareness and to delineate the underlying bases for them.

### Management and Treatment of Anosognosia

Unfortunately, large controlled trials of specific management and treatment methods for subjects with anosognosia after closed head injury are not yet available. A number of approaches are reported to be symptomatically useful (36–41). These include *explicit* techniques in which therapists have subjects self-assess and then perform straightforward, quantifiable tasks and help them to measure assessment-performance discrepancies, *implicit* techniques in which subjects are asked to perform in both preserved and deficient areas in order to experience the contrast between these abilities, and techniques involving *external and off-line feedback*, such as videotaping and later viewing task performance, and reviewing it in a group setting with performance assessment from other group members. Related to the external/off-line method is *intervention based on third person assessments*, in which patients make judgments about pictured scenarios in which others fail to perform tasks, preselected to resemble their impairments (42). Although reinforcement with these methods has traditionally been behavioral, positive results have been reported when increased accuracy of self-assessment is reinforced with monetary rewards (43).

A general difficulty with these clinical reports, however, is that although patients' awareness of deficit may have improved, the effect on daily living activities has not been well-studied. In at least one instance, there was a failure of the improved self-awareness to generalize to untrained tasks (38). Therefore, further studies are needed to identify the most effective interventions for anosognosia after TBI. In typical practice, such interventions are team-based and often require continued efforts by educated caregivers after hospital discharge.

## INTELLECTUAL FUNCTIONING

Measures of intellectual functioning are frequently employed in the neuropsychological assessment of brain-injured patients to ascertain a broad range of cognitive capacities (44, 45). Although several instruments have been designed for the purpose of evaluating intelligence, the Wechsler scales are currently favored by most clinicians. The Wechsler Adult Intelligence Scale has several important features:

1. It surveys a broad range of verbal and nonverbal cognitive abilities with standardized instructions and materials

2. Test items are presented in ascending difficulty and usually discontinued after a certain number of incorrect responses, allowing for assessment of many different abilities without undue frustration for patients
3. The scale provides multiple scores for comparison such as verbal, performance and full scale IQ, and index scores for verbal comprehension, perceptual organization, working memory and processing speed
4. Interpretation of multiple subtest and composite scores is possible through extensive normative data that provide statistical comparisons, enhancing the strong reliability and validity indicators of the scale.

Interpretation of IQ tests requires highly trained clinical expertise particularly because there is no single or specific profile of intellectual impairment that results from brain damage (46). From available studies, however, it is possible to identify several common patterns of findings related to TBI effects, as follows:

1. A generalized pattern of intellectual decline is most likely to be observed in patients whose TBI is at least moderate to severe (47, 48).
2. The Wechsler Processing Speed Index is particularly sensitive to brain dysfunction, due mainly to the sensitivity of the digit-symbol coding and symbol search subtests. In contrast, other subtests (e.g., Matrix Reasoning, Vocabulary) appear resistant to the incremental effects of TBI (47, 49).
3. A large discrepancy between Verbal and Performance IQ scores is not always synonymous with brain damage; nor does it necessarily imply damage to one hemisphere versus the other. For example, a lower Performance IQ may be related to slowed visuomotor processing rather than right hemisphere damage per se, and a lower Verbal IQ may be related to impaired attention and concentration rather than left hemisphere damage per se. However, discrepancies of 15 points or more deserve close scrutiny for cognitive dysfunction (50, 51) as these differences are reaching statistically improbable levels for typical cognitive functioning. This entails ruling out other premorbid or concurrent causes of test impairment and supporting any inferences about localized brain damage (e.g., left or right hemisphere, frontal or temporal cortical) with additional specific indicators.
4. In reasoning about and explaining any left vs. right hemisphere disparities in intellectual processing, investigators have emphasized that the left hemisphere tends to fundamentally process information sequentially whereas the right hemisphere engages in more simultaneous information processing (51). Thus, left vs. right hemisphere deficits, at least as expressed through verbal vs. performance IQ score differences, should not be interpreted as simply verbal vs. visuospatial differences; rather, they may reflect different levels and approaches to information processing.
5. In studies of localized cerebral damage, left hemisphere injuries often result in lower digit span and arithmetic subtest scores, whereas picture arrangement deficiencies have been associated with right hemisphere lesions (52).
6. Impairment on the block design subtest has been associated with damage to the parietal lobes regardless of the side of cerebral dysfunction (46).
7. Vocabulary and picture completion subtests have been employed in estimating premorbid intellectual functioning because of their robust resistance to brain injury (49, 52).
8. Deficits on the similarities subtest has been associated predominantly with left frontal injury because of its reliance on verbal concept formation and abstraction (51, 53).
9. In interpreting intellectual test scores and patterns, the important contributions of unique personal attributes must be assessed including educational level, premorbid functioning, learning disability, cultural/linguistic factors and others that are likely to affect IQ test scores.

The foregoing summary should not be considered immutable; rather, clinicians engaged in assessing intellectual functioning among TBI patients utilize these principles to guide interpretation and hypotheses about related functional deficits, their causes and their remediation. Similarly, the cognitive strengths observed in IQ testing may point clinicians in the direction of harnessing intact patient abilities to compensate for possible limitations. In our clinical experience, we do not rely on one sign of TBI as being sufficient for rendering diagnosis. Similarly, the presence of atypical IQ scores by itself should not be taken to suggest cerebral impairment without further investigation. For individuals with unusual IQ profile scores, review of their school testing records can disclose significant pre-existing discrepancies in verbal and mathematical/spatial abilities. Competent neuropsychological evaluations take many factors into account as part of understanding TBI effects. IQ scores, therefore, should not be considered in isolation from measures of attention, memory, language, etc; similarly, test data should not be emphasized in the absence of a clear patient history, neurological evaluation and related data from other service providers.

## MEMORY

Learning and memory are among the most fundamental and important capacities that underlie human development



and adaptation. The neurobiological bases of how we acquire and subsequently retain vast amounts of information and experiences remain enigmatic though there is increasing understanding of the neural structures and processes that mediate functional memory systems. In scientific and clinical studies of TBI there is viable evidence for both alterations to memory-related structures and disruption of memory processing. The effects of post-traumatic memory impairments can be disabling and significantly limit an individual's ability to live independently, handle a job, and interact productively with others (54). Subjective complaints of memory impairment after TBI are quite common, even among those with mild TBI and good medical recovery (55). Although not always substantiated by objective memory testing, physiological brain changes underlying such complaints have been verified in some scientific studies but not others. The controversy arises in part from the wide individual variability in the effects of TBI on learning and memory abilities. Differences in patient sampling (e.g., consecutive series vs. patients referred for assessment) and in how learning and memory are assessed may lead to dissimilar results and conclusions. Differences in the length of time post-injury, age, and severity of TBI can also contribute to contrasting outcomes. Complicating effects of chronic pain, sleep disturbance, depression, stress due to loss of income etc. are known to contribute to learning and memory problems, and must be considered in both etiology and treatment plans. Despite these many cautions, reliable correlation has been found between memory performance and brain volumetric measures in the temporal lobe of adults with mild TBI (56). Specifically, decreased hippocampal and temporal white matter volumes were significantly related to memory impairment. Despite normal MRI or CT imaging in 15 of 20 patients with mild TBI, Umile et al. (57) reported that dynamic brain imaging (including SPECT and PET) detected abnormalities in 18 of the 20 patients, with 15 of 20 having abnormalities in the temporal lobe, primarily the hippocampal region. There are also functional imaging data suggesting that the brain activity patterns of TBI patients become altered during tasks of memory retrieval. Specifically, patients engaged increased levels of frontal, anterior cingulate and occipital activity while showing reduced right dorsomedial thalamic activation and attenuated hemispheric asymmetry that was characteristic of controls (58).

### Post-Traumatic Amnesia

Post-traumatic amnesia (PTA) refers to the immediate and dramatic amnesic effects of TBI. Patients can be described as *confused, agitated, repeating questions*, and *disoriented* in this acute/post-acute phase. PTA is defined as the period during which patients are neither encoding nor retaining any new information and experiences, and can

last from a few moments to several weeks and even months after TBI. Although patients are awake and alert during this period, they subsequently recall little to no information regarding the accident and such post-traumatic events as transportation to the hospital, medical evaluation, and even visits of family members. Patients with PTA are disoriented to time, place and reason for hospitalization, and may even think that they are at school or in their hometown. As described previously, they may show anosognosia during this period as well as a range of behavioral difficulties and agitation.

PTA is variable in both extent of amnesia and pattern of recovery. It is considered a general marker of neurological impairment and in most cases gradually improves. Sometimes the term 'shrinking post-traumatic amnesia' is used to refer to the gradual reduction in severity and temporal extent of amnesia (in both retrograde and anterograde spheres). PTA can be assessed with standardized instruments such as the Galveston Orientation and Amnesia Test (59). Recovery of orientation and short-term memory can be reliably predicted from early daily screening and is generally predictive of functional independence upon discharge (60, 61). It is important during this period to rule out contributing effects of sleep disturbance, pain medications, and other complicating factors on post-traumatic attention and memory deficits.

An interesting implication of PTA concerns its relationship to post-traumatic stress disorder (PTSD). That is, does loss of consciousness and memory after TBI necessarily preclude the development of PTSD symptoms that typically involve the re-experiencing of the traumatic events as well as heightened emotion with anxiety and avoidance behaviors. If the event cannot be remembered, can PTSD symptoms still be possible? Turnbull, Campbell and Swann (62) examined the inter-relationship in 53/371 TBI cases. Results indicated that those with traumatic memories of the TBI event ( $n = 26$ ) reported the highest psychological distress followed by those with no traumatic memories ( $n = 14$ ) who reported less severe and non-intrusive symptoms. Reviews by Bryant (63) and Harvey et al. (64) have generally favored the view that PTA and PTSD can co-exist though in ways that may be different than in non-TBI PTSD cases. The latter review underscored a number of caveats, related either to imprecise criteria for TBI and/or limited assessment of stress-related symptoms (PTSD and acute stress disorder). Further research is needed to clarify the causes and management of these co-morbid conditions.

### Information Processing Aspects of Memory

Memory is neither a unitary nor an automatic process. Although there is individual variation in learning styles, cognition and interests that affects subsequent retention, there are several well-standardized tests of learning

and memory that permit identification of specific memory impairments. Information processing approaches to memory and the brain have identified 3 principal aspects: *encoding*, *consolidation* and *retrieval*. Encoding typically refers to the acquisition of new information and experiences through sensory-perceptual and attentional mechanisms. Encoding is believed to be mediated by several cortical/cortical sensory-perceptual systems together with attentional/executive resources that are allocated according to information load, difficulty, prior knowledge etc. Consolidation pertains to biological mechanisms that are necessary to maintaining a memory trace, thought to involve interactive processing between cortical sensory association areas and limbic system structures, particularly the hippocampus and related medial temporal lobe areas. Retrieval refers to the recovery of stored information either through recall or recognition processes. The neural basis of retrieval remains unclear but may involve executive processes mediated by the prefrontal cortex for search and comparison of familiarity. Given this model of memory and the diversity of neural structures and connections that subserves memory, it becomes easier to understand how memory complaints may be so common after TBI, since large scale coordination of attentional, sensory-perceptual, limbic and executive processing systems is usually required.

Studies investigating TBI and memory continue to show diverse results. While some studies have identified principally encoding deficits, others have identified consolidation and retrieval deficits (65, 66). Curtis et al. (67) suggested that subgroups of memory impaired TBI patients can present with mainly consolidation or retrieval deficits. Particularly in patients with mild TBI, memory impairments may not be apparent on some standardized testing and become evident only under certain conditions such as when patients must divide attention during the encoding phase (68). The latter investigators reported that patients with severe TBI can also present with variable memory results, depending upon whether they attended to the target stimuli or distracting stimuli during encoding. There are a number of other cognitive and learning parameters that can affect memory retention in patients. For example, strategies of clustering similar semantic information (e.g., chunking) can improve verbal retention, while spaced repetition of words can also contribute to more effective learning (69). An important clinical guideline that is emerging from extant literature is the realization that interactive effects of processing speed, working memory and episodic memory impairments may combine to influence learning and memory capacities in naturalistic settings (70). In addition to the importance of cognitive remediation strategies for these deficits, some researchers have suggested that pro-cholinergic medications may be helpful in recovery (71, 72).

## CONFABULATIONS AND DELUSIONS

TBI can cause both confabulations and delusions. These disorders lie at the interface of memory, self-awareness/self-monitoring, visual perceptual and executive function abilities after TBI and occur as direct effects of brain injury and as associated features of organic psychoses. Some patients show confabulations within the context of significant amnesia, attempting to fill in gaps of memory loss with overlearned knowledge about themselves and others. This kind of confabulation is thought to involve a combination of amnesia and disinhibited responding, usually associated with temporal and frontal dysfunction. Several delusional misidentification syndromes have been described, centering around altered ability to recognize people and the belief that people are disguising themselves in some way. These have been associated with combined damage to frontal (usually bilateral) and right posterior hemisphere regions. Examples include Capgras syndrome, defined as the impaired belief that someone well known to the patient has been replaced with a look-alike imposter (also described as reduplicative paramnesia) (73), and Fregoli syndrome in which the patient believes that a stranger (e.g., another patient or a staff member) is actually a familiar person (such as their mother) (74). Confabulations and delusions generally resolve over time, but are also known to persist chronically. Challenging patients' false beliefs is often not helpful in recovery and family members as well as providers often must accommodate these fixed beliefs. A single delusion can occur or there may be several co-occurring delusions, not necessarily inter-related. Misidentification and delusional syndromes can occur after TBI without other features of psychosis.

## SPATIAL COGNITION

Spatial cognition subserves a variety of adaptive behaviors, from navigation within diverse environments to spatial-related attention, memory and reasoning. Spatial cognition is obviously critical to daily activities such as driving, ambulation, dressing, self-care and keeping track of items maintained in home and work settings. TBI infrequently causes the striking hemispatial neglect syndrome often associated with right parietal lobe damage, but can lead to changes in attention to spatial cues, visuomotor scanning that underlies spatial search, constructional praxis, and learning/memory of places as well as various spatial patterns and complex scenes (66, 75, 76). Exploratory deficits and other motor-intentional spatial disorders commonly occur after TBI, associated with medial frontal cortical dysfunction and hypokinesia (77). Most often, spatial cognitive deficits associated with TBI have not been singled out per se, but rather discussed within the context of attention,

intelligence, memory and executive functions. Spatial representational and spatial-motor dysfunction after TBI have been less fully investigated.

### CHEMICAL SENSES

TBI can dramatically affect both olfaction and taste. Olfactory deficits have been associated with multiple types of trauma to the head as well as trauma to the nasal cavity, olfactory epithelium, and the olfactory nerve as it travels through the cribriform plate to the olfactory bulb. Brain pathophysiology from inflammation, white matter shearing, hemorrhage, contusion and other effects can cause particular damage to the main olfactory structures of the brain including the olfactory bulb, tract, and interconnected subcortical and piriform cortical regions in the basal and medial aspects of the frontal and temporal lobes (78). In a comprehensive study of 268 patients with TBI, studied at a specialty smell and taste center, Doty and colleagues (77) reported that 66.8% showed anosmia (complete loss of smell) and 20.5% demonstrated microsmia (partial loss of smell). The incidence of these deficits was higher than other reports probably because of specialty center referral patterns. Performance was based on scores from the University of Pennsylvania Smell Identification Test, a 40-odorant scratch and sniff, multiple choice recognition test. About one-half of the cases suffered head trauma from motor vehicle accident, with head trauma from falls the second most likely cause. Follow-up testing of 66 patients, varying from 1 month to 13 years later (mean follow-up period was 5.5 years, with mean age 41.25 years, and the sample 55% male), showed that 36% improved slightly while 45% experienced no change and 18% worsened in their olfactory deficit. Three patients actually regained normal olfaction although none had anosmia to begin with. The incidence of parosmia (olfactory distortions) decreased from 41% to 15.5% over an 8-year follow-up period. Parosmias varied from transient to intermittent to persistent in severity. There were no significant effects of age, sex or time since injury on olfactory deficits. Other changes in olfaction include decreased threshold, hallucination (usually associated with post-traumatic epilepsy), and decreased recognition memory.

Taste can be affected by TBI in a variety of ways, although usually not as severe as olfaction. Quantitative changes in gustation include altered threshold levels and decreased intensity of taste that are often described as ageusia or hypogeusia (80). Occasional increased sensitivity or hypergeusia can occur as well. Changes in taste are typically measured in relationship to detection and recognition of the four basic taste stimuli: salty, sweet, sour, and bitter. Qualitative changes in gustation are often described as onset of unpleasant tastes such as bitterness, metallic and even rancid, and as a loss of typical taste

preferences. Deems et al. (81) reported that 18% of all taste problems evaluated at a specialty smell and taste clinic were related to trauma. These disorders are generally not amenable to treatment once other modifiable causes have been ruled out (e.g., oral hygiene, sinus, oral secretions, toxic exposures, smoking). Subcortical-cortical gustatory regions and pathways are less vulnerable to damage from head trauma than olfaction. Complaints of decreased taste can be related in many cases to olfactory loss, leading to decreased flavor detection and perception rather than gustatory deficit per se.

### EXECUTIVE FUNCTIONS

Executive functions encompass cognitive and emotional processes that underlie many aspects of human adaptation, adjustment, and achievement. These processes have often been defined in terms of complex cognitive activities such as planning, judgment, decision-making and anticipation that require the coordination of multiple sub-processes to organize behaviour and achieve particular goals. Associated cognitive operations include working memory, prospective memory, strategic planning, cognitive flexibility, abstract reasoning and self-monitoring. Executive functions have also been implicated in the goal-directed *regulation* of attentional resources, sensory-perception, and actions in order to manage transitions from one activity to another throughout the day and across diverse settings (8, 82–85).

The neural systems involved in executive functions include the prefrontal cortex most prominently, together with interconnected neural circuitry forming prefrontal-cortical and subcortical networks. Some of these networks have been described under the terms *dorsolateral*, *orbital* and *medial* (86, 87). The dorsolateral prefrontal circuit is thought to mediate many higher cognitive aspects of behaviour such as abstract reasoning, planning and working memory. The orbital prefrontal circuit has been implicated mainly in social and emotional aspects of behavior including certain kinds of decision-making, theory of mind, emotional-based learning and social judgment. The medial prefrontal circuit has been related to motivational and attentional processes including initiation, inhibition and maintenance of behavior. In studies of TBI-related pathology, orbital and medial regions of the prefrontal cortex have been found to be especially vulnerable to damage by mechanisms of shearing and stretching of fibers as well as direct injury from impact against the irregular base of the skull. The orbital-medial prefrontal region is especially affected by strong blunt impact as well as physical acceleration/deceleration forces. Applied force vectors and tissue compliance influence the intensity of the coup, countercoup, angular and rotational forces that stretch and lacerate brain tissue centrifugally,

from midline sagittal aspects (i.e., medial and orbital prefrontal cortex impacting against the lamina cribrosa and the roof of the orbit as well as against the wing of the sphenoid bone) toward the surface of the cortex (lateral prefrontal cortex) and the deep connections with the striatum, thalamus and other subcortical nuclei such as the amygdala.

TBI-related damage to prefrontal neural circuits has been linked to the variety of executive function deficits. Impairments on measures of working memory (e.g., Paced Auditory Serial Addition Test), divided attention and sequencing (e.g., Trail Making), verbal associative fluency, learning and memory as well as planning and set shifting have been reported, even in cases after mild TBI (88, 89). Some clinical disorders such as distractibility and impulsivity have been found to be related to measured attentional and executive function deficits (90, 91). Significant correlations between measures of executive functions and regional cerebral glucose metabolism have been found in the mesial and lateral prefrontal regions and the cingulate gyrus. Interestingly, the correlations were evident despite the absence of detectable structural lesions on brain MRI. These findings confirmed those reported previously by Goldenberg et al. (92) who also noted correlation of executive measures with reduced blood flow in the thalamic region. Hence, impairments of executive functions may be related not only to focal traumatic lesions of the prefrontal cortex but also to white matter disconnection (i.e., diffuse axonal injury) of prefrontal-related networks that link to the thalamus and other important cortical and subcortical regions.

Some behavioral disorders after TBI have not been linked to cognitive deficits per se and may be due to alterations in emotion-related processing. For example, Rolls et al. (93) reported that patients with ventral frontal damage after TBI had particular difficulty in reward-based contingency learning. That is, after successfully learning an initial stimulus-reward association, they were impaired in both reversal learning (when the stimulus signalling reward was reversed) and in extinction learning (when the stimulus no longer signalled reward). The impairments were correlated to surveyed behavioral deficits that included disinhibition, social difficulties, lack of initiative and perseveration. Interestingly, the behavioral deficits were not correlated with verbal IQ, paired associate learning or Tower of London performance. Emotion processing may also be an integral part of decision-making capacities when one must rely on judgment of chance and probability of consequences such as gambling. This has been operationalized into a standardized task (The Iowa Gambling Task) in which subjects must learn to choose cards from stacks that are rigged to have different levels of risk and pay-off, varying from high risk-high win to low risk-low win (94). Patients with ventral frontal damage performed poorly on this task, choosing high risk

options that led to huge losses. Furthermore, many did not generate the anticipatory skin conductance responses that might typically signal risk-taking effects. Another facet of emotion-related processing involves recognition of common forms of emotional expressions. Hornak et al. (95) showed that ventral frontal damage from head trauma (and other etiologies as well) was associated with deficient recognition of emotional facial expressions and correlated with subjective emotional change and social behavior of patients.

Both focal and diffuse frontal lesions disrupt activities of daily living (ADL) and executive impairment may represent a main component of ADL failure (96, 97). In particular, executive abilities of planning, self-monitoring and self-correction, decision-making and judgement are considered critical for independent, adaptive functioning within real world settings (98). Deficits of inattentiveness, mental slowing, impulsivity, and lack of prospective memory can all contribute to functional impairments after TBI. The impact of such impairments can be viewed as damaging a complex cognitive-emotional *macrostructure* or *managerial knowledge unit* (including strategic planning, procedural memory, working memory) that underlies most multi-step requirements of real life, such as meal preparation or a recreational activity (97, 99). Meal preparation or going to a movie may well be more difficult than many cognitive tasks presented during a formal cognitive testing session in the laboratory because of the need to impose structure and invest executive resources in planning, implementing and accomplishing the many aspects of the task (82, 83, 99, 100). In cognitive testing the patient typically is administered a single problem with instructions, learning trials may be short, initiation is prompted and feedback is often given at the end of the task. Certainly it is not the same in real world settings, where situational constraints, priorities and requirements are not always clear, and success depends on timely, internally-generated and self-monitored processing without the benefit of feedback. Most neuropsychological tests do not specifically explore strategic planning, competitive skills, or prospective memory. A notable exception to this is the experimental Strategic Management Simulation technology that has shown promise in detecting executive impairments in TBI patients with good medical recovery and few neuropsychological test deficits (101). An important priority in both assessment and linkage to cognitive remediation is the development of further paradigms that tap multiple problem solving variables in real time and with varying degrees of structure and feedback.

### Social Cognition and Behavior

Humans are naturally social creatures, born to live and thrive within social settings with many complex forms

of interaction that have emotional coloring and context. Hence, an important facet of human cognition and executive functioning extends beyond the strictly intellectual endeavors of planning, concept formation, and problem-solving to domains such as metacognitive thinking, social skills, moral beliefs, personality traits, and “theory of mind”, a special faculty of the human brain that mediates interpretation and appreciation of other people’s feelings and mental states (8, 102, 103). Fronto-temporal damage from TBI can lead to dramatic alterations of conduct, personality, and psychosocial integration, at times leaving most cognitive and sensory-motor functions relatively intact. From a clinical standpoint, there is often a spectrum of social-behavioral symptoms associated with TBI rather than definite syndromes. Some patients become puerile, profane, facetious, irresponsible, irascible, and aggressive as forms of social disinhibition. Others lose spontaneity, initiative, curiosity, and develop mental and behavioral inertia as forms of abulia and apathy (104). Still others develop lack of awareness and insight, loss of creativity and emotional vitality. Some of these deficits are expressed as loss of pragmatic aspects of communication, loss of empathy and inability to understand and appreciate sarcasm, jokes, irony, and other vital social communication tools (105, 106). Although many of these social-emotional deficits are difficult to objectively evaluate and measure, they are important and problematic sequelae of TBI that must be evaluated and managed. The combined use of clinical interview with patient and family members and behavioral inventories can uncover many of these deficits. Experimental measures of social judgment, theory of mind abilities, social knowledge and emotion-related processing are beginning to shed light on deficits underlying these real-life problems and are increasingly targeted in experimental intervention programs.

### SUMMARY

Cognitive impairments after TBI often present significant challenges for recovery and return to premorbid levels of occupational and social functioning. In early stages, patients’ lack of awareness of their deficits (anosognosia), impaired self-regulation, and post-traumatic amnesia constitute major limitations to participation in rehabilitation services and safety. Often there is a combination of attentional, memory, perceptual, processing speed, executive function and social-emotional deficits that require multimodal therapy services and a gradual return to independent daily activities. Cognitive and social-emotional deficits are frequently slower to recover than physical injuries and require outpatient therapy services with medical follow-up care. Education of caregivers is particularly important for monitoring and continued remediation of

such impairments within home and community settings. When cognitive deficits remain persistent, individualized therapy is usually required combining aspects of skill retraining, compensatory strategies, and environmental supports to optimize functional cognitive capacities.

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# 43

## Neuropsychological Assessment and Treatment of TBI

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**C**linical neuropsychologists are professionals within the field of clinical psychology who have special expertise in the area of brain-behavior relationships. According to the National Academy of Neuropsychology (NAN) definition (1), clinical neuropsychologists use “psychological, neurological, cognitive, behavioral, and physiological principles, techniques, and tests to evaluate patients’ neurocognitive, behavioral, and emotional strengths and weaknesses and their relationship to normal and abnormal central nervous system functioning.” Results from comprehensive evaluations are utilized for identification and diagnosis of neurobehavioral disorders, prognostication, development of treatment plans, and rehabilitation of individuals with neurologic conditions, health problems, neurodevelopmental disorders, cognitive problems, learning disorders, and psychiatric conditions. Many neuropsychologists are also responsible for the development and implementation of individual, group, and family therapy and education programs. This chapter will review guiding principles for neuropsychologists, the process of neuropsychological assessment and report writing, the contribution of neuropsychological assessment to the development of treatment recommendations, and neuropsychologist’s role in rehabilitation and treatment. This chapter further strives to explore the role of neuropsychology in rehabilitation and a holistic approach to patient care.

### PRINCIPLES GUIDING THE PRACTICE OF CLINICAL NEUROPSYCHOLOGY

Neuropsychologists play a key role in the evaluation and treatment of individuals with traumatic brain injury (TBI). Some view neuropsychology as a purely technical field with practitioners focusing on cognitive testing and functional neuroanatomy. More recently, neuropsychologists have taken a holistic perspective on practice focusing on issues of emotional adjustment, family functioning, and treatments to help patients return to normal life.

A set of guiding principles has been developed to help neuropsychologists develop a more holistic practice. Consideration of the following principles can help clinicians more efficiently achieve positive outcomes and effect greater levels of client satisfaction:

- empower patients and their families to take an active role in the evaluation and treatment process
- believe that people with neurological disabilities are more like people without neurological disabilities
- convey honesty and caring in personal interactions to form an adequate foundation for a strong therapeutic relationship
- develop practical plans for rehabilitation and explain rehabilitation techniques in language that patients, families, and interdisciplinary professionals are likely to understand



- help patients and their families understand the common neurobehavioral sequelae of brain injury and the typical recovery course
- recognize that change is inevitable and help the patient and family develop plans to deal with changes as they arise over time
- remember that every patient is important and deserves to be treated with respect
- remember that patients and families often have different perspectives; consider their individuality when formulating treatment approaches
- be willing to refer to other professionals if a case extends beyond personal areas of expertise and clarifies roles of various treatment providers.

**TABLE 43-1**

*The Caring, Understanding, Respecting, and Trust-Building Checklist*

- Review the patient's chart before seeing them; try to remember important details, and bring the details into your conversations.
- Go beyond your job description, at least sometimes.
- Ask the patient if they have questions or want to mention something that has not come up in conversation; answer their questions in language they can understand.
- When you can't help, refer to others who can.
- Discuss your ideas about helping the patient and your plans to do so.
- When asked by the patient, communicate to significant others about the patient's needs and care.
- Listen carefully.
- Give the patient time to finish what they are saying.
- Paraphrase what the patient says to convey your understanding.
- Maintain eye contact and face the patient when talking to them.
- Be on time for appointments and apologized on the rare occasions when you are not.
- Address patients by their proper surname (Mr., Mrs., or Ms.) unless instructed by them to do otherwise.
- Frequently inquire about the patient's needs, priorities, and perceptions of progress.
- Ask the patient for ideas about how to make things better and try to use their ideas.
- Carefully explain and discuss the limits of your expertise.
- Do what you say you will when you say you will.
- Respect the patient's right to confidentiality.
- Acknowledge when circumstances prevent you from doing what you agreed to and discuss acceptable alternatives.

Adapted from *The Brain Injury Handbook: A Guide for Rehabilitation Providers for Improving Therapeutic Relationships* (Kreutzer, Kolakowsky-Hayner, & West, 1999) (2).

To facilitate a positive and effective practice, many rehabilitation professionals employ a variety of trust-building behaviors with their patients. Table 43-1 displays a checklist of behaviors, which neuropsychologists and other rehabilitation professionals are encouraged to incorporate into their standard practice.

## COMPREHENSIVE NEUROPSYCHOLOGICAL ASSESSMENT

Comprehensive neuropsychological evaluation typically involves clarification of the referral question, review of records, clinical interviews, behavioral observation, and administration of standardized measures. Standardized measures are used to assess cognitive, academic, neurobehavioral, and emotional functioning. In addition, the impact of the acquired brain injury on the family, pain, substance abuse, vocational potential, motivation, effort, judgment, and safety are also areas of emphasis in neuropsychological assessment. The following sections will describe these evaluation techniques in more detail.

### Referral Question

The first step in neuropsychological assessment is identifying issues of concern and clarifying referral questions. Doing so allows selection of relevant assessment methods. Directly answering the referral source's questions and addressing their concerns is a hallmark of a beneficial neuropsychological report.

Referral sources often request information in three areas: (1) information pertaining to diagnosis, prognosis, and neuropsychological, neurobehavioral, and emotional functioning; (2) information about functional abilities, including level of independence and academic and vocational functioning; and (3) information about treatment and rehabilitation needs. Tables 43-2, 43-3, and 43-4 depict common referral questions encountered by neuropsychologists in each of these three areas. The variety of referral questions highlight the variety of complex issues and questions which neuropsychologists are often asked to address in their assessments. Answering these questions appropriately necessitates comprehensive, holistic assessment. They also provide insight into potential recommendations and treatment needs.

### Records Review

Thorough review of the records is the foundation of the evaluation process, providing guidance for the interview, test selection, and treatment planning. In addition, familiarity with records allows the examiner to ask the patient relevant questions during the initial interview and communicates to the patient that the examiner is well-prepared

TABLE 43-2

*Referral Questions Regarding Cognitive, Emotional, and Neurobehavioral Functioning*

- Is there any evidence of preexisting cognitive, emotional, or neurobehavioral difficulties? Describe levels of functioning in each area relative to preinjury.
- How has the neurological injury impacted their cognitive, emotional, or neurobehavioral functioning?
- Are current symptoms consistent with preexisting difficulties, psychological disorder, brain injury, or a combination of factors?
- Is there evidence that emotional/psychological difficulties contribute to cognitive deficits?
- To what extent does pain or unresolved physical problems contribute to emotional or cognitive impairments?
- Is the patient at risk of harming him/herself or others?
- Is there evidence of posttraumatic stress disorder, depression, anxiety, or other psychological disorders?
- Within each area of cognitive, intellectual, and psychomotor functioning, compare the patient's performance to the normal population. Which areas would you consider to be relative strengths and which areas would you consider to be weaknesses?
- Compare the patient's level of functioning in each area to the patient's last evaluation. Which skills have improved, declined, and remained stable? Identify potential factors which may have contributed to improvements or limited change.
- What is the prognosis for future improvements or declines?
- When will it be helpful to evaluate the patient again? for what purposes?
- Is the patient eligible for special services, programs, or benefits?

and interested in the patient's well being. Review of medical, psychological, criminal, academic, and vocational records is strongly recommended. Review of medical and rehabilitation records provides information about pre- and post-injury history of health problems and treatment. Information pertaining to mechanism of injury, injury severity, injury-related cognitive and physical sequelae, and rehabilitation services may also be obtained. Pre- and post-injury mental health records provide an invaluable source of information about long-standing emotional issues and substance misuse and post-injury emotional, neurobehavioral, and personality changes. Mental health records also provide information about treatments and medications which have been effective. Criminal records may elucidate difficulties with authority, antisocial behavior, mental health issues, substance abuse problems, and litigation history.

In reviewing school records, the neuropsychologist gains information about history of learning difficulties, academic potential, and information about the patient's

TABLE 43-3

*Referral Questions Pertaining to Adaptive, Educational, and Vocational Functioning*

- Is the patient safe to drive? If not, what are the patient's needs with respect to driving evaluation, driver's training, and instruction in use of public transportation? Is the patient eligible for transportation services for persons with disabilities?
- Is the patient safe to live independently? If not, what supervision level or alternative living arrangements are recommended?
- Is the patient competent to manage their finances?
- Can the patient manage their medication independently?
- Please provide information about the patient's judgment and safety.
- How will the patient's neurobehavioral status impact parenting?
- What is the patient's potential for academic and vocational success?
- How has the injury impacted the patient's academic and vocational potential?
- Is the patient able to manage part-time or full-time work schedule?
- What kinds of training, accommodations, and interventions are most likely to increase their potential for academic or vocational success in the current school/work environment?
- Can the patient succeed in the present academic/work environment? Should an alternative academic placement or employment opportunity be considered?
- How will the patient's neurobehavioral status impact their ability to interact with coworkers, customers, family, friends, etc.?
- Identify which neuropsychological factors are primarily contributors to functional impairments.
- Is there evidence that emotional/psychological difficulties contribute to functional impairments?

strengths and weaknesses. Vocational records review includes examination of performance reviews, job descriptions, and information about wage history, attendance records, grievances, and disciplinary actions. Based upon review of vocational records, the neuropsychologist has the opportunity to ascertain pre- and post-injury work experience, habits, attitudes, and accomplishments. In addition, records review provides information about the patient's ability to function within structured environments, response to authority figures, and interpersonal skills. Academic and vocational history provides the basis for making recommendations about vocational and academic potential, optimal work/school settings, and appropriate accommodations. In addition, review of academic and vocational records provides an opportunity for estimating patients' premorbid or expected level of functioning.

**TABLE 43-4**  
**Referral Questions Pertaining to Treatment Issues**

- What types interventions have the potential to benefit the patient (e.g., medication, rehabilitation services, psychotherapy, support group, vocational rehabilitation, etc.)?
- Provide information about reasonable treatment goals, priorities for intervention, optimal frequency of services, potential service providers, and associated costs.
- Which factors will affect the patient's ability to benefit from rehabilitation interventions and treatment? Are there interventions that would minimize limiting factors (e.g., pharmacologic, compensatory)?
- Is the patient a good candidate for individual, group, marital, or family therapy?
- What is the patient's prognosis for improvement with and without intervention?
- Is the family a good support system? How are family members helping the patient or contributing to present difficulties?
- What are the family's expectations regarding recovery and the patient's ability to return to previous activities? What are the family's needs with respect to education about the recovery process?
- What support and education programs would benefit family members? Describe potential service providers, optimal frequency of services, and associated costs.

Establishing the premorbid level of functioning provides the basis for judging current levels of impairment.

### Behavioral Observations

Behavioral observation during the course of interview and testing affords the examiner with the opportunity to assess behaviors, which are not readily tapped by quantitative assessment devices. Table 43-5 depicts information that is typically gathered through behavioral observation. Observation across different settings, by different observers, and at different times is optimal. Interviewing patients in their home or current living situations is an excellent means of obtaining information about how patients react in their home environments. If home-based observation is not possible, family members and caregivers may be able to provide additional information about behavior observed in the home. Neuropsychologists also gather information about behaviors from members of the interdisciplinary team members who may have the opportunity to observe the patient in other settings.

### Clinical Interview

The clinical interview provides a valuable sample of behavior. The examiner has the opportunity to observe

how the patient interacts and responds to questions. In addition, the clinical interview affords an opportunity for clarifying information from the records, gathering historical information, and ascertaining primary presenting concerns. During the clinical interview, special care is taken to collect the following information: presenting complaints; family/caregiver concerns; injury information; postconcussive symptoms; academic and vocational history; family and social functioning; medical and psychological history; history of prior TBIs; and current daily living situation and functional capabilities. Every effort is made to interview the patient and one or more family members/caregivers. If in-person interview with family members is not possible, telephone interview may be a viable option. Interviewing employers, teachers, and treating providers is also valuable.

### Quantitative Assessment

Quantitative neuropsychological assessment findings provide a useful complement to data gathered through behavioral observation and clinical interview. Quantitative assessment provides the opportunity to gather data about neuropsychological functioning in a standardized way, allowing the examiner to make comparisons to normative data and to make comparisons over time with repeated testing (3). In determining which assessment instruments to use, neuropsychologists consider several factors. First, comprehensive assessment is multidimensional and multimethod, covering a range of functioning areas using a variety of measures to assess each area. Second, tests are selected with emphasis placed upon problem areas endorsed by the patient, his or her family, and the referral source. Third, measures are chosen based upon ease of completion and administration time whenever possible. Finally, in determining which tests to use, neuropsychologists consider the test reliability and validity, normative samples, and research findings specific to brain injury.

This section does not provide encyclopedic knowledge about the function and process of quantitative neuropsychological assessment. On the contrary, we purport to offer a broad overview of the topic emphasizing the importance of evaluating patients as multi-faceted beings with significant pre-injury histories, interpersonal relationships, emotional reactions to injury and so forth. Those interested in comprehensive reviews of this subject are encouraged to peruse Lezak's text, *Neuropsychological Assessment* (3) and the chapter entitled, "Neuropsychological Evaluation of the Patient with Traumatic Brain Injury" in *Rehabilitation of the Adult and Child with Traumatic Brain Injury* (4).

### Evaluation of Cognitive and Academic Functioning

Following TBI, individuals commonly experience cognitive difficulties. Comprehensive assessment of cognitive

**TABLE 43-5**  
*Behavioral Observations Relevant to Neuropsychological Assessment*

GENERAL OBSERVATION AREA	SPECIFIC AREAS TO ASSESS
Appearance	<ul style="list-style-type: none"> <li>• Dress</li> <li>• Physical condition</li> <li>• Hygiene</li> <li>• Eye contact</li> </ul>
Motor abilities and stamina	<ul style="list-style-type: none"> <li>• Gait/ambulation</li> <li>• Reaction time</li> <li>• Quality of movements</li> <li>• Signs of restlessness/agitation</li> <li>• Fatigue and stamina</li> </ul>
Affect	<ul style="list-style-type: none"> <li>• Range</li> <li>• Appropriateness to situation and content</li> <li>• Consistency with reported mood</li> <li>• Level of frustration tolerance</li> <li>• Signs of anxiety, grief, depression, euphoria, or emotional withdrawal</li> <li>• Emotional lability</li> </ul>
Communication	<ul style="list-style-type: none"> <li>• Speech quality (e.g., rate, volume, tone)</li> <li>• Fluency, articulation, intelligibility, and spontaneity of speech</li> <li>• Word-finding problems/anomia</li> <li>• Grammar and vocabulary</li> <li>• Auditory comprehension abilities</li> <li>• Ability to understand and carry out task instructions</li> </ul>
Thought patterns	<ul style="list-style-type: none"> <li>• Organization of thoughts</li> <li>• Evidence of hallucinations, delusions, or paranoia</li> <li>• Ability to remain on topic and other unusual thinking patterns (e.g., tangentiality, circumstantiality, derailment, paraphasia, clanging, neologisms, blocking, perseveration)</li> <li>• Flexibility or rigidity in thinking</li> <li>• Appropriateness of responses</li> </ul>
Attitude toward examiner and testing	<ul style="list-style-type: none"> <li>• Cooperation and interest level</li> <li>• Consistency of effort</li> <li>• Persistence</li> <li>• Openness to questions</li> <li>• Level of comfort</li> </ul>
Attitude toward self/level of self-awareness	<ul style="list-style-type: none"> <li>• Level of self-confidence</li> <li>• Awareness of errors and error correction</li> <li>• Reaction to successes and failures</li> <li>• Accuracy of performance rating</li> <li>• Insight and level of awareness</li> <li>• Attainability of goals</li> </ul>
Reactions to test items	<ul style="list-style-type: none"> <li>• Level of frustration tolerance</li> <li>• Expressed concern about task difficulty</li> <li>• Increase or decrease in effort with increasing task difficulty</li> <li>• Persistence</li> </ul>
Work habits and approach to testing	<ul style="list-style-type: none"> <li>• Response rate, response latency, and processing speed</li> <li>• Deliberate versus impulsive responding</li> <li>• Planning and organization abilities</li> <li>• Problem-solving approach to tasks</li> <li>• Flexibility in shifting between tasks</li> <li>• Handwriting accuracy</li> <li>• Reaction to praise</li> </ul>

**TABLE 43-6**  
**Tests and Their Corresponding Area of Functioning**

FUNCTIONING AREA	TEST(S)
<b>Academic Skills</b>	
Arithmetic Calculation	Arithmetic (Wide Range Achievement Test - Third Edition: WRAT3); Numerical Operations (Wechsler Individual Achievement Test – 2nd edition: WIAT-II)
Arithmetic Reasoning	Arithmetic (Wechsler Adult Intelligence Scale–Revised & 3rd edition: WAIS-R & WAIS-III); Mathematics Reasoning (WIAT-II)
Reading Comprehension	Gray Oral Reading Test-Revised (GORT-R); Reading Comprehension (WIAT-II); Test of Reading Comprehension – Third Edition (TORC-3)
Word Reading	GORT-R; Pseudoword Decoding and Word Reading (WIAT-II); Reading (WRAT3); TORC-3
Spelling	Spelling (WRAT3); Spelling (WIAT-II)
Writing	Spelling (WRAT3); Spelling and Written Expression (WIAT-II)
<b>Attention and Concentration</b>	
	Continuous Performance Test; Dementia Rating Scale (Attention scale); Digit Span and Digit Symbol (WAIS-R & WAIS-III); Letter-Number Sequencing (WAIS-III & WMS-III); Mental Control (Wechsler Memory Scale-Revised & 3rd edition: WMS-R & WMS-III); Paced Auditory Serial Addition Test (PASAT); Spatial Span Forward and Backward (WMS-III); Speech Sounds Perception Test, Rhythm Test, and Trail Making Test: Parts A and B (Halstead-Reitan Battery: HRB); Stroop Color Word Test; Symbol Digit Modalities Test (SDMT)
<b>Motor and Sensory Functions</b>	
Speed and Dexterity	Finger Tapping Test (HRB); Grooved Pegboard
Grip Strength	Hand Dynamometer (HRB)
Coordinated Bilateral Movement	Luria Motor Tests
Hand-Eye Coordination	Digit Symbol (WAIS-R & WAIS-III); Grooved Pegboard; Luria Motor Tests; SDMT (written); Trail Making Test: Parts A & B (HRB)
Sensory & Sensorimotor	Tactile Perception, Tactile Form Recognition, Tactile Localization, and Fingertip Writing (HRB); Tactual Performance Test (TPT; HRB)
<b>Nonverbal Memory</b>	
Immediate	Benton Visual Retention Test; Corsi Block Test; Dementia Rating Scale (Memory scale); Family Pictures and Faces (WMS-III); Motor Free Visual Perception Test; Visual Reproduction (WMS-R & WMS-III)
Delayed	Dementia Rating Scale (Memory scale); Family Pictures and Faces delay (WMS-III); Recognition Memory Test; Rey Osterrieth Complex Figure Test (ROCF); Visual Reproduction (WMS-R & WMS-III)
Learning	Digit Symbol (WAIS-R & WAIS-III); Spatial Span (WMS-III); SDMT
Incidental Learning	Coding (WISC-III); SDMT; TPT (Memory and Location)
<b>Verbal Memory</b>	
Immediate	California Verbal Learning Test: CVLT (Trial I); Logical Memory and Verbal Paired Associates (WMS-R & WMS-III); Rey Auditory Verbal Learning Test: RAVLT (Trial I); Word Lists (WMS-III)
Delayed	CVLT (delay and recognition); Logical Memory and Verbal Paired Associates delay (WMS-R & WMS-III); RAVLT (delay and recognition); Word Lists delay (WMS-III)
Remote Memory and Fund of Information	Information (WAIS-R & WAIS-III)
Learning	CVLT; RAVLT
<b>Visual Based Skills</b>	
Visuoperception and Visual Reasoning	Digit Symbol, Object Assembly, Picture Completion, and Picture Arrangement (WAIS-R & WAIS-III); Hooper Visual Organization Test; Judgment of Line Orientation Test; Line Bisection Test; Motor Free Visual Perception Test; SDMT (oral & written); Visual Form Discrimination Test

TABLE 43-6 (continued)

FUNCTIONING AREA	TEST(S)
Visuomotor & Visuoconstruction	Digit Symbol, Block Design and Object Assembly (WAIS-R & WAIS-III); ROCF; SDMT; Trail Making Test A and B
<b>Language Skills</b>	
Vocabulary	Clinical Interview; Vocabulary (WAIS-R & WAIS-III)
Oral Fluency	Controlled Oral Word Association Test
Naming	Boston Naming Test
Expressive Language	Aphasia Screening Test (HRB); Boston Diagnostic Aphasia Examination; Clinical Interview; Oral Expression (WIAT-II)
Receptive Language	Behavioral observation of instruction following; Clinical Interview; Listening Comprehension (WIAT-II); Token Test
<b>Reasoning and Judgment</b>	
Verbal Reasoning	Comprehension and Similarities (WAIS-R & WAIS-III)
Nonverbal Reasoning	Category Test (HRB); Picture Arrangement (WAIS-R & WAIS-III); Ravens Progressive Matrices; Trail Making Test B (HRB); Wisconsin Card Sorting Test
Judgment of Safety	Comprehension (WAIS-R & WAIS-III); Independent Living Scales; Judgment and Safety Screening Inventory (JASSI) – Patient and Informant Versions
Self-Awareness	Clinical Interview; Judgment and Safety Screening Inventory (JASSI), comparison of patient and family responses; Neurobehavioral Functioning Inventory (NFI), comparison of patient and family responses

and academic functioning can help elucidate deficits. Areas which are typically assessed in comprehensive evaluation of cognitive and academic functioning include: academic skills, attention and concentration, motor abilities, sensation, learning and memory, visuoperception, visuoconstructional abilities, language, and reasoning. Table 43-6 depicts specific tests and the corresponding areas of functioning assessed. The reader is referred to Lezak's (3) seminal text on neuropsychological assessment for further information about tests which are commonly used to assess cognitive and academic functioning.

#### *Assessment of Emotional, Personality, and Neurobehavioral Functioning*

Neurobehavioral and personality changes are common following TBI. In addition, survivors typically have difficulty adjusting to injury-related changes, increasing the risk of emotional difficulties. As such, comprehensive neuropsychological evaluation involves assessment of neurobehavioral, emotional, and personality functioning. Table 43-7 describes several measures which are commonly administered to assess these areas of functioning.

Concern has been expressed that measures of emotional and personality functioning have limited utility for patients with TBI. First, many instruments were developed specifically for people with psychiatric difficulties, not for those with neurological disorders. Many individuals with TBI may be diagnosed with psychiatric disorders

secondary to the overlap between sequelae of TBI and psychiatric symptoms. Witol and colleagues (6) caution clinicians to consider the contributions of TBI when interpreting the results of measures of emotional and personality functioning. The Neurobehavioral Functioning Inventory (NFI; 10) and the Neurobehavioral Rating Scale (NBRS; 11) were developed for use with TBI populations, and may be good alternatives. Second, reliance on self-report is difficult following TBI secondary to difficulties with self-awareness. As such, clinicians seek out corroborating information from family members and records review. Finally, many measures are long and require at least a sixth grade reading level. Many individuals experience reading comprehension problems, visual disturbances, pain, and attention and concentration problems. Each of these injury-related sequelae can negatively impact patients' abilities to respond to the questionnaires. If concerns about a patient's ability to respond to the questionnaire emerge, clinicians may wish to consider clinician-rated measures such as the NBRS and the Hamilton Depression Rating Scale (HDRS; 8).

#### *Evaluation of Judgment and Safety*

Safety is a common area of concern for families and referral sources following TBI. Questions often arise surrounding safety in the following situations: driving, living alone, working, and managing finances and medications. In assessing safety issues, evaluating patient's

**TABLE 43-7**  
*Measures Used to Assess Emotional, Personality, and Neurobehavioral Functioning*

MEASURE	BRIEF DESCRIPTION
Beck Depression Inventory (BDI)	The BDI is a 21-item, self-report measure designed to detect the presence and severity of depression symptoms (5). The multiple-choice format requires a sixth grade reading level. Repeated administrations permit monitoring of treatment effects. Notably, the BDI emphasizes the vegetative symptoms of depression which may be consistent with TBI and medical illness (6).
Brief Symptom Inventory (BSI)	The BSI, a shortened version of the Symptom Checklist-90-R, is a 53-item self-report measure, which is designed to evaluate the severity of psychiatric symptoms (7). A sixth grade reading level is required. Few studies have been conducted with TBI populations. Witol and colleagues (6) expressed concern about the possibility neurobehavioral symptoms would be labeled as psychiatric.
Hamilton Depression Rating Scale (HDRS)	The HDRS is a 17-item screening instrument, which was designed to assess the cognitive, emotional, and physical symptoms of depression (8). The measure is completed by the clinician during the clinical interview with the patient and family and records review. As such, the measure is useful for screening depression in individuals who have limited reading abilities or vision problems which preclude reading. There is limited research examining the validity of using the HDRS with TBI populations. Witol and colleagues (6) expressed concern that many of the items are consistent with neurobehavioral sequelae of TBI.
Minnesota Multiphasic Personality Inventory – 2nd Edition (MMPI-2)	The MMPI-2 is a 567-item, self-report measure of personality and emotional functioning in adults (9). A 6th grade reading level is required, but audiotaped versions are available. Concern has been expressed about overpathologizing of individuals with TBI on the MMPI-2. Witol and colleagues (6) urge clinicians to consider the contributions of TBI when interpreting the results of the MMPI-2.
Neurobehavioral Functioning Inventory (NFI)	Developed for use with a TBI population, the NFI is an 83-item measure which was designed to examine the frequency of neurobehavioral difficulties post-injury (10). The measure can be administered in a self-report format or orally. Patient and family versions are available, allowing for comparison of responses. Normative data, based upon age and injury severity, is available. Information is gathered about functioning in six domains: depression, somatic symptoms, memory/attention, communication, aggression, and motor abilities.
Neurobehavioral Rating Scale (NBRS)	Adapted from the Brief Psychiatric Rating Scale, the NBRS was designed to assess behavioral and emotional symptoms, which are commonly exhibited post-TBI (11). The 27-item scale is completed by a clinician based upon observations during an interview. Items are rated on a scale from 1 (not present) to 7 (extremely severe). Witol and colleagues (6) assert that the NBRS is an extremely useful tool for assessing neurobehavioral functioning acutely.

judgment is critical. To assess judgment and safety, the examiner may ask patients and their family members about daily functioning. For example, with regard to driving, information may be gathered about recent accidents or traffic violations and about patient and family members' concerns. Medication issues include forgetting

medications and not taking medications as prescribed. With respect to financial management, the examiner may ask about bounced checks, late or missed bills, and utilities being turned off.

The Judgment and Safety Screening Inventory (12) was designed to assess judgment and safety concerns in

**TABLE 43-8**  
*Methods Used to Assess Substance Use*

MEASURE	BRIEF DESCRIPTION
Addiction Severity Index (ASI)	The ASI assesses recent and lifetime alcohol and illicit drug use difficulties and gathers information regarding legal issues, medical and vocational history, and family/social functioning (21). The ASI has been found to have good reliability and validity (22); however, research on the ASI and acquired brain injury populations is very limited.
Brief Michigan Alcoholism Screening Test (B-MAST)	The B-MAST, a shortened version of the MAST, contains 10 of the original 25 MAST items and is highly correlated with the MAST (23). The B-MAST has been found to be useful in the detection of alcohol abuse among individuals with TBI (20).
CAGE	The CAGE is a four-question screening tool, which is easily administered and scored. Each question follows a yes/no format. Two or more positive responses are suggestive of alcohol problems. The CAGE has been shown to be highly effective in detecting alcohol abuse in the general population (24) and in individuals with TBI (20).
Michigan Alcoholism Screening Test (MAST)	The MAST is a 25-item screening questionnaire that focuses on lifetime problems and consequences of drinking in the areas of social, vocational, and family functioning (25).
Quantity-Frequency-Variability Index (QFVI)	The QFVI is a self-report measure, with patient and informant versions. The QFVI classifies drinking behavior in one of five categories: abstinent, infrequent, light, moderate, or heavy (26, 27). The QFVI has been shown to be effective in assessing pre- and post-injury alcohol use among survivors of TBI (28). Concordance rates between family members' and patients' reports on the QFVI have been found to exceed 90% (29).
Substance Abuse Subtle Screening Inventory (SASSI)	The SASSI is a 78-item, self-report alcohol and drug abuse assessment instrument, which has been found to have high sensitivity and specificity when used with the general population. However, the SASSI appears to be less effective in detecting substance abuse problems among individuals with TBI (30).

the following areas: travel; financial management; interpersonal functioning; food and kitchen; use of appliances, tools, and utensils; household issues; medications and alcohol; fire safety; and firearm safety. Respondents are asked to identify their concern level (none, little, much, or very) about different aspects of each functioning area. Space is provided for open-ended responses from patients and other informants. Patient and informant versions allow for comparisons between respondents.

### *Substance Abuse Assessment*

Substance abuse is a significant problem for individuals with TBI and occurs more frequently among survivors of TBI than in the general population (13–16). In a comprehensive review study, Corrigan (17) indicated that approximately two thirds of individuals with TBI have a history of substance abuse pre-injury, and one third to one half of individuals hospitalized are intoxicated at the time of injury. In a study by Hall and colleagues (18), approximately 30% of participants with a brain injury were alcohol dependent whereas 20% were drug dependent at two years post-injury.

Given the significance of this problem among survivors of TBI, substance abuse screening is an important part of comprehensive neuropsychological evaluation. Substance abuse assessment involves administration of standardized assessment measures and thorough review of records. Measures designed to assess substance abuse in the general population are often used to assess pre- and post-injury substance use in persons with acquired brain injury. Research reveals that composite measures are helpful in diagnosing and treating substance abuse problems among persons with brain injury (19). Assessment measures frequently used include the Michigan Alcoholism Screening Test (MAST), Brief Michigan Alcoholism Screening Test (B-MAST), CAGE, Quantity-Frequency-Variability Index (QFVI), Addiction Severity Index (ASI), and Substance Abuse Subtle Screening Inventory (SASSI). Table 43-8 provides descriptions of each measure. Overall, research suggests that the CAGE or B-MAST are more effective screening instruments for TBI populations and less time-consuming than the SASSI and ASI (20).

Self-report measures are easily administered and relatively inexpensive, and as such, they are often the



cornerstones of substance abuse assessment. However, self-report measures are limited due to their reliance upon individuals' willingness and ability to disclose information accurately. Patients may be reluctant to admit the extent of alcohol or drug use. Patients with memory problems or limited self-awareness may also be unreliable historians (29). Family members' reports may also be inaccurate secondary to minimization or denial of problems, personal substance abuse history, perceptions about substance use, or lack of information regarding the patient's use (30). Given the aforementioned limitations, accurate assessment of substance use may be compromised if one relies predominantly on information provided by one source. To address these limitations, neuropsychologists solicit information from a variety of informants, including family members, caregivers, and employers. Records review also allows for corroboration of informant and patient reports.

### *Pain Assessment*

Pain, a common complaint of individuals who have sustained TBI, often contributes to cognitive deficits and negatively impacts quality of life secondary to activity restrictions. Individuals' response to pain varies significantly based upon the meaning of pain to the individual and the impact of pain on their life. Thorough pain assessment may include administration of standardized measures, such as the McGill Pain Inventory (31) and visual analog scales (32). Information is gathered about pain intensity, frequency, duration, quality, location, date of onset, history of pain problems, family history, and treatments and their effectiveness. In addition, behaviors which exacerbate and improve pain are important to assess. Patients are often asked to rate their pain on a 1 (no pain) to 10 (extreme pain) scale throughout the assessment in order to establish if poor performances are related to pain. During the evaluation, examiners are alert to pain behaviors (e.g., shifting in seat, rubbing areas of pain focus) and to medication side effects (e.g., fatigue). The reader is referred to the chapter in this book entitled, "Pain Assessment and Management," by Drs. Zasler, Nicholson, Martelli, and Bender for detailed information about the assessment and treatment of pain among individuals with TBI.

### *Assessment of Motivation and Effort*

Comprehensive neuropsychological assessment typically incorporates evaluation of patients' motivation and effort during the evaluation. As a general practice, patients are often encouraged to exert maximum effort during the testing process to reduce concerns about malingering (33). When there is a question of malingered neuropsychological impairment, practitioners have several techniques to discourage and identify such activity. Neuropsychologists look for consistency in performance across tests, consistency of

test performance and presenting complaints with those expected given injury severity, and consistency between observed behaviors and presenting complaints.

Neuropsychological and psychological tests may be used to assess legitimate versus malingered memory impairments or exaggerated symptoms. Mittenberg, Azrin, Millsaps, and Heilbronner (34) found a pattern of scores on the Wechsler Memory Scale-Revised (35) that differentiated individuals instructed to malingere head trauma symptoms from patients with head injury. Discrepancy between predicted and obtained scores on the Wechsler Adult Intelligence Scale-Revised (36) may be used to discriminate between patients with TBI and those producing insufficient effort (37).

Specialized tests developed specifically for detection of malingering are available for inclusion in neuropsychological test batteries, including the following: Portland Digit Recognition Test (38), Recognition Memory Test (39), Rey 15-Item Test (40), Test of Memory Malingering (41), and the Word Memory Test (42). Normative data on the F(p) Scale of the MMPI also aids in the identification of unusual response patterns suggestive of insufficient effort or symptoms exaggeration (43).

Secondary gain issues are important to consider, including revenge, attention seeking, escape from responsibility, and pending lawsuits, Worker's compensation hearings, or disability benefit hearings. History of litigation and benefit seeking should be ascertained during interview and records review. The reader is referred to the chapter in this book entitled, "Assessment of Response Bias," by Drs. Martelli, Zasler, and Bender for a thorough review of assessment techniques for evaluating motivation and effort.

### *Vocational Assessment*

Research suggests that a majority of persons with moderate or severe TBI are unable to sustain employment (44-47). Vocational issues are a primary concern for patients and their families, and referral sources frequently list return to work among their primary concerns for patients. Referral questions often focus on individuals' readiness to return to work, potential work capacity, and needed accommodations and rehabilitation services. Prognostication about vocational potential should be based upon thorough return to work assessment and comprehensive neuropsychological evaluation revealing strengths and limitations. Comprehensive assessment reveals potential obstacles to successful return to work, including cognitive deficits, emotional issues, interpersonal difficulties, transportation issues, anger management problems, and pain and other physical symptoms.

Areas which are commonly assessed in comprehensive assessment include the following: (1) job responsibilities, including special training required, equipment used,

and interpersonal interaction with co-workers and customers; (2) conditions set by employer regarding return to work; (3) the patient's perceptions about obstacles to working and about their ability to return to work on a part-time or full-time basis; (4) transportation requirements for the job; (5) work schedule issues (e.g., hours required, over time, swing shift work, possibility of working part-time, flexibility of position, openness to accommodations); (6) safety issues on the job, including history of prior injuries on the job; (7) work-place response to others with injuries and disabilities; (8) relationship with supervisor; (9) supervisor's knowledge of the injury and extent of injury-related sequelae; (10) pre-injury work history; (11) patient perceptions about job security; and (12) the patient's career goals, desire to return to work, and willingness to consider other job options. In addition, consideration of the nature of the job in question is valuable. Individuals tend to be most successful returning to work in family-owned or small businesses, which are supportive and allow for accommodations.

### *Family and Caregiver Assessment*

As the length of hospital and rehabilitation stays decrease (48, 49), family members have had to take on the principal caretaking role soon after injury. Caregiving places significant burden on the family. Research reveals that caregiving family members are at risk for emotional difficulties (50–58). Given the importance of the family's role in caring for the survivor, assessment of the impact of injury on the family is critical to ensure they have the support needed to continue performing their vital role. Family and caregiver assessment should center around gaining an understanding of the impact of injury on emotional functioning, relationship quality, financial situation, life plans, quality of life, and daily responsibilities (e.g., work, child care, household responsibilities). In addition, clinical neuropsychologists often explore existing supports and consider additional support needs. Written recommendations that include options for increasing family supports are extremely beneficial. Special care should be taken to help the caregiving family member(s) understand that they will be unable to support the survivor if they do not take care of themselves and seek assistance in managing their increasing responsibilities. The reader is referred to James Malec, Ph.D.'s chapter in this text entitled, "Family and Caregiver Issues and Interventions," for information about issues related to assessment and treatment of family members and caregivers.

### **Comparison to Premorbid Functioning**

Neuropsychologists are often asked to determine whether or not the injury resulted in cognitive, academic, neurobehavioral, or emotional impairments. Determining deficits requires comparison of current functioning to pre-morbid functioning. Three methods may be employed to

estimate premorbid functioning. First, several indicators are highly correlated with intelligence, and as such, provide an estimate of premorbid functioning. These indicators include grades, scores on standardized testing, and educational and vocational attainment. Review of records and clinical interview are avenues of gathering this information. Second, some measures of cognitive functioning (e.g., single-word reading) are highly correlated with intelligence and are typically not affected by TBI (59). Scores on these standardized measures will likely be comparable to premorbid levels of functioning. Finally, within the "best performance method," the highest test scores obtained during comprehensive neuropsychological evaluation are considered in the estimation of pre-injury abilities (3).

## **PROGNOSTICATION AND TREATMENT PLANNING**

### **Prognostication**

Questions about future prognosis are typically among the primary questions posed by referral sources. As such, clinical neuropsychologists are often called upon to provide information about long-term academic, vocational, and independent living potential. In addition, questions are often posed about an individual's likelihood of benefiting from rehabilitation services and potential treatment benefits. Thorough review of the research literature on outcomes following TBI provides the foundation for prognostic estimation. Several factors need to be considered when making predictions about an individual's outcome, including age, premorbid level of functioning, injury type and severity, additional injuries (e.g., orthopedic), pre-existing medical and psychological issues, extent and chronicity of deficits, daily functioning, and availability of support services and interventions (3).

### **Recommendations and Treatment Planning**

Comprehensive neuropsychological assessment culminates in the development of practical, feasible recommendations and the development of treatment plans. The goal is to develop recommendations and identify interventions, which will enhance patients' and families' well being and optimize functioning. Referral for medical follow-up, psychological services, psychiatric intervention, support, vocational/academic assistance, and other rehabilitation services in the community are commonly included. Compensatory strategies to address impairments are typically provided. Repeated neuropsychological testing is often suggested to monitor progress or deterioration. Based upon findings from re-evaluation, amendments may be made to the existing treatment plan. Table 43-9 depicts recommendations that may be provided to address problems in a variety of functional areas.

**TABLE 43-9**  
*Post-Injury Problem Areas and Aample Recommendations*

FUNCTIONAL AREA	RECOMMENDATIONS
<b>Academic skills</b>	
Arithmetic	<ul style="list-style-type: none"> <li>• use a calculator for all but the most basic mathematical operations; check work carefully; rely on family for assistance with financial management</li> </ul>
Reading comprehension	<ul style="list-style-type: none"> <li>• use chapter headings to outline material; take notes and highlight or underline key words while you are reading; use self-sticking notepaper to create indexes in the reading material to facilitate reviewing information; use the PQRST method (preview, question, read, study, test)</li> </ul>
Spelling	<ul style="list-style-type: none"> <li>• use an electronic spelling aid or word processing spell checker; purchase a portable electronic spell checker for home use; spell the word out loud, or mouth each letter as you spell the word to help focus your attention as you write; keep a small speller's dictionary near where you write; use index cards to make flash cards of words you find yourself missing often and test yourself; play Scrabble; work cross-word and other puzzles</li> </ul>
Writing	<ul style="list-style-type: none"> <li>• focus on quality versus quantity; allow ample time for task completion; dictation; remedial training</li> </ul>
<b>Attention and concentration</b>	
	<ul style="list-style-type: none"> <li>• reduce distractions (e.g., ear plugs, sit facing wall, clear desk before beginning work); avoid interruptions (e.g., use 'do not disturb' sign); use self-coaching to stay on task; schedule breaks throughout the day; avoid multi-tasking; before changing tasks, record information about stopping point</li> </ul>
<b>Motor/sensory functioning</b>	
Coordination and motor slowing	<ul style="list-style-type: none"> <li>• occupational and physical therapy; fitness training; sports and recreational activities; pace tasks; allow adequate time for task completion and transition between tasks; organize environment for efficiency (e.g., gather all needed materials prior to initiating project); set realistic timelines for task completion</li> </ul>
Vision	<ul style="list-style-type: none"> <li>• neuro-ophthalmologic evaluation; corrective lenses; vision therapy; use large print reading materials and thick pen when writing notes to be read by client; audiotape instructions/reading material; make sure there is appropriate light; avoid glare</li> </ul>
Hearing	<ul style="list-style-type: none"> <li>• audiology examination; ask others to speak loudly and enunciate clearly; hearing aids</li> </ul>
Smell	<ul style="list-style-type: none"> <li>• smoke detectors; label and date perishable foods</li> </ul>
<b>Learning and memory</b>	
	<ul style="list-style-type: none"> <li>• present information in many forms (e.g., auditory, visual, kinetic); use to-do lists, calendars, memory notebook, and other assistive devices; repeat information; use mnemonics and imagery; demonstrate tasks; record and replay information; break tasks down into small steps and introduce new steps as earlier steps are accomplished</li> </ul>
<b>Visually based skills</b>	
	<ul style="list-style-type: none"> <li>• use a blank piece of paper or fold the sheet to mask extraneous details on a page; use a straight edge, ruler, or finger to follow a line of text; always check work in the same order; describe a design or task in words rather than rely on a mental image; take part in activities which require hand-eye coordination</li> </ul>
<b>Language</b>	
Instruction following	<ul style="list-style-type: none"> <li>• improve instructional format (e.g., short, simple sentences); simplify or reduce variety of tasks; reduce distractions; provide instructions in multiple formats; shaping</li> </ul>
<b>Judgment and safety</b>	
Judgment and safety issues	<ul style="list-style-type: none"> <li>• consider supervised living situations; 24-hour supervision; respite for family; seek feedback from others before beginning a task</li> </ul>
Problem solving	<ul style="list-style-type: none"> <li>• teach structured problem solving; develop and maintain mentor relationship; ask client how they plan to approach task prior to beginning</li> </ul>

TABLE 43-9 (continued)

FUNCTIONAL AREA	RECOMMENDATIONS
Driving	<ul style="list-style-type: none"> <li>take precautions to maximize safety (e.g., avoid driving in inclement weather or traffic, drive with licensed driver, take breaks on long trips, drive familiar routes, drive only when well rested, reduce distractions); driving evaluation; driver's training; training in use of public transportation; exploration of other transportation options (family, friends, neighbors, and area resources);</li> </ul>
Financial management	<ul style="list-style-type: none"> <li>rely on family to assist with financial management; use an organizer with dated slots and place bills in slots one week before they are due; record due dates for bills in a calendar or planner; use a calculator; check work carefully; take care of challenging tasks only when well rested and distractions are minimized</li> </ul>
Medication management	<ul style="list-style-type: none"> <li>use a compartmentalized medication box, distributing medication in appropriate compartments at the beginning of the week; set an alarm to cue when to take medication</li> </ul>
<b>Fatigue/sleep problems</b>	<ul style="list-style-type: none"> <li>promote sleep hygiene (e.g., regular sleep schedule, limit caffeine/exercise before bed); medication consultation (stimulants and sleep medication); consider sleep study; adjust work schedule; schedule breaks; schedule most challenging tasks at times of peak energy level</li> </ul>
<b>Emotional issues</b>	
Depression	<ul style="list-style-type: none"> <li>supportive psychotherapy; medication management; enhance support network; increase activity level and participation in pleasant activities; encourage focus on progress; avoid comparisons to the past; monitor sources of stress</li> </ul>
Frustration, irritability, and anger problems	<ul style="list-style-type: none"> <li>stress management and relaxation training; anger management; assertiveness, conflict resolution, and social skills training; medication management</li> </ul>
Feeling misunderstood by others	<ul style="list-style-type: none"> <li>communication and social skills training; educate client about how to discuss injury with others; education of coworkers, employers, and family; supportive psychotherapy; support group; enhance social support</li> </ul>

## DIFFERENTIAL DIAGNOSIS

Patients with TBI present for assessment and treatment with myriad cognitive, behavioral, emotional, and somatic symptoms. Differential diagnosis is often the culmination of a comprehensive neuropsychological assessment. Differential diagnosis requires a breadth of knowledge about the spectrum of the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (60) conditions and proficient interviewing skills. Information about the onset, nature, intensity, and duration of symptoms provides valuable insights into conditions, which should be considered as possible diagnoses. Oftentimes, the confirmation of a diagnosis follows long-term evaluation and treatment of the patient. Exacerbation or abatement of symptoms, as well as the emergence of additional problems, are monitored to facilitate differential diagnosis.

Neuropsychological evaluators and rehabilitation treatment providers incorporate a multitude of data collection strategies to glean pertinent information for differential diagnosis. Clinicians may enlist assistance from family members, friends, or significant others in order to procure thorough medical, social, and psychiatric patient

and family history. Unstructured, semi-structured, or structured interviews are often utilized to this end. The *Structured Clinical Interview for DSM-IV Axis I Disorders—Clinical Version* (61) is an assessment tool available to practitioners for determining pre and post-injury psychological difficulties. Glenn (62) advised conducting a structured search in order to best discover etiology and recommended the following information be ascertained: pre-injury diagnosis, neuropsychological disorders, sensorimotor disorder, medical disorders, adverse effects of medication, reactive mood and anxiety disorders, and sleep disorders.

There is often considerable overlap between symptoms of medical and psychological disorders. For example, cognitive impairments are typical consequences of most neurological conditions, including frontotemporal dementia and TBI (63). However, impairments in cognition are often evident in individuals with psychiatric disorders, including major depressive disorder and anxiety disorders. As such, differentiation between the etiologies of cognitive impairments may be challenging.

Differentiation between pre-existing conditions and post-injury complications is often critical to forming an

accurate diagnosis and to planning effective treatment. Premorbid psychological or personality disorders, learning disabilities, drug or alcohol problems, and medical conditions (e.g., cerebrovascular disease, hypertension, diabetes, epilepsy, prior TBI) are potential mediating variables that commonly influence the course of a TBI. In conducting a comprehensive evaluation, neuropsychologists attempt to tease out premorbid problems from current injury-related complications and sequelae. In order to assist clinicians in differentiating between premorbid problems and post-injury complications, Table 43-10 provides referral questions to consider during comprehensive neuropsychological assessment.

Identification of comorbid conditions is one of the principal aims of comprehensive neuropsychological assessment. Psychological comorbidities are quite common after a TBI. Hibbard and her colleagues (64) found two or more Axis I diagnoses post-TBI, representing 44% of their sample. Depression and anxiety disorders (e.g., PTSD, OCD, panic disorder, GAD) were the most frequently cited post-injury affective problems of this sample. Researchers have found that approximately 60% of individuals with a TBI meet criteria for major depression at some point after a brain injury (64). Research indicates the frequency of reported emotional difficulties is directly proportional to injury severity, except in the most severe cases of TBI (65). Table 43-11 depicts common comorbidities encountered in the clinical practice of patients with TBI.

Neuropsychological evaluators consider the impact of comorbidities such as mood disorders or psychosis on

patients' assessment findings. For example, conditions that alter mental status (e.g., delirium, vegetative states, or active hallucinations) may invalidate results of assessment. Screening with measures such as the Mini-Mental Status Examination (66) or the Minnesota Multiphasic Personality Inventory-II (67) is recommended. These instruments help to rule-out potentially confounding factors of diminished consortium or significant affective disturbance, respectively. Table 43-12 provides a list of test measures least and most susceptible to the affect slowed mental processing and/or psychomotor performance often observed with certain mood disorders.

Mild head injury offers unique challenges to evaluators in terms of differential diagnosis than moderate and severe neurological damage. Clear physiological

**TABLE 43-11**  
*Common Comorbidities*

- Adjustment Disorder with Anxiety or Depressed Mood
- Adjustment Disorder with Mixed Emotional Features and Disturbed Conduct
- Major Depressive Disorder
- Mood Disorder due to General Medical Condition
- Personality Change Secondary to General Medical Condition
- Polysubstance Abuse
- Post-traumatic Stress Disorder
- Substance Abuse or Dependence

**TABLE 43-10**  
*Questions to Facilitate Differentiation Between Premorbid Problems and Injury-Related Sequelae*

- Did patient have problems with substance misuse prior to the TBI?
- Did the individual have a pre-injury personality disorder?
- Was the patient receiving mental health treatment for a mood disorder or other psychological problem before the injury?
- Did the patient have pre-existing learning difficulties?
- Were pain or sleep problems apparent prior to the patient having a TBI?
- How was the patient's daily functioning prior to the injury? Explore areas such as relationships, occupational or educational pursuits, and recreational activities.
- Have others noticed a change in the patient's functioning since the injury?
- When did emotional difficulties or substance use issues arise?

**TABLE 43-12**  
*Tests Least and Most Susceptible to Affect of Mood Disorders*

LEAST SUSCEPTIBLE	MOST SUSCEPTIBLE
Category Test	Symbol Digit Modalities Test
WAIS Verbal Subtests Vocabulary Comprehension Similarities	WAIS Performance Subtests Block Design Digit Symbol-Coding
Rey-Osterrieth Complex Figure Test	Trail Making Test: Parts A & B
Wide Range-Achievement Test Reading Spelling	Grooved Pegboard Test
Token Test	Controlled Oral Word Association Test

consequences of serious brain injury are unquestionable, such as positive CT or MRI findings. For mild brain damage, however, hard neurological signs of injury may not be present. Comorbid problems with somatic functioning may complicate differential diagnosis after mild head injury. Practitioners are encouraged to be familiar with

difficulties associated with somatic problems. According to the DSM-IV (60), there are a number of distinct disorders with a physical presentation, including Pain Disorder, Hypochondriasis, Somatization Disorder, and Conversion Disorder. Table 43-13 depicts highlights of the DSM-IV criteria for each of these diagnoses.

**TABLE 43-13**  
*DSM-IV Diagnoses and Associated Criteria for Selected Disorders*

DSM-IV DIAGNOSIS	CRITERIA
Pain Disorder	<ul style="list-style-type: none"> <li>• pain reported at one or more anatomical sites</li> <li>• pain is sufficient in severity to warrant clinical attention</li> <li>• pain causes significant distress or impairment in functioning</li> <li>• psychological factors have an important role in onset, severity, exacerbation, or maintenance of pain</li> <li>• symptoms or deficits are not better accounted for by another mental condition (i.e., mood, anxiety, or psychotic disorder) and does not meet criteria for Dyspareunia</li> <li>• symptoms or deficits are not intentionally feigned</li> </ul>
Hypochondriasis	<ul style="list-style-type: none"> <li>• preoccupation with fears of having a serious disease</li> <li>• fear is often based on the person's misinterpretation of bodily symptoms</li> <li>• preoccupation persists despite appropriate medical evaluation and reassurance</li> <li>• belief is not of delusional intensity and is not restricted to a circumscribed concern about appearance</li> <li>• preoccupation causes clinically significant distress or impairment in functioning</li> <li>• duration of the disturbance is at least 6 months</li> <li>• preoccupation is not better accounted for by Generalized Anxiety Disorder, Obsessive-Compulsive Disorder, Panic Disorder, a Major Depressive Episode, Separation Anxiety, or another Somatoform Disorder</li> </ul>
Somatization Disorder	<ul style="list-style-type: none"> <li>• history of many physical complaints beginning before age 30 years</li> <li>• complaints must continue for several years and result in treatment being sought</li> <li>• after appropriate investigation, each of the physical symptoms cannot be fully explained by a known medical condition or the direct effects of a substance (e.g., a drug of abuse, a medication)</li> <li>• when there is a related general medical condition, the physical complaints or resulting impairment are in excess of what would be expected from the history, physical examination, or laboratory findings</li> <li>• patient reports or displays symptoms at any time during the course of the disturbance as described below: <ul style="list-style-type: none"> <li>○ four pain symptoms</li> <li>○ two gastrointestinal symptoms</li> <li>○ one sexual symptom</li> <li>○ one pseudoneurological symptom</li> </ul> </li> </ul>
Conversion Disorder	<ul style="list-style-type: none"> <li>• one or more symptoms or deficits affecting voluntary motor or sensory function</li> <li>• symptoms are suggestive of a neurological or other medical condition and may not be intentionally produced or feigned <ul style="list-style-type: none"> <li>○ symptom cannot, after appropriate investigation, be fully explained by a general medical condition, or by the direct effects of a substance, or as a culturally sanctioned behavior or experience</li> <li>○ symptom causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation</li> <li>○ symptom is not limited to pain or sexual dysfunction, does not occur exclusively during the course of Somatization Disorder, and is not better accounted for by another mental disorder</li> </ul> </li> </ul>

## NEUROPSYCHOLOGICAL REPORT WRITING

Communicating results from the neuropsychological assessment to referral sources, treating providers, patients, and their families is a critical task for neuropsychologists. If test results are not communicated effectively, the utility of the entire assessment process comes into question. When writing a helpful report, neuropsychologists consider the following:

1. Review records thoroughly to ensure that historical information, pre-existing conditions, and injury severity are understood and considered in formulating impressions and recommendations.
2. In formulating diagnostic impressions, consider the impact of pre-existing conditions, psychological and emotional issues, motivation, effort, self-awareness, and pain.
3. Write reports in a language that patients and lay people can understand, avoiding use of jargon.
4. Tailor reports to each specific patient rather than being generic.
5. Write and disseminate reports in a timely fashion. Review test results with the patient and discuss findings in a meaningful way. Encourage the patient and his or her family to ask questions.

6. Take special care to ensure reports address and answer the referral source's questions and concerns.
7. Consider the patient's and family's concerns and the meaning of the injury to the patient during report development.
8. Consider the patient's reactions to test findings and impressions, and take special care to ensure the presentation of the findings and conclusions will be palatable to the patient.
9. Highlight strengths as well as deficits.
10. Translate test results into recommendations which will make patients' lives better.

Although practitioners are encouraged to develop unique reports which are specific to each patient, structure is an important way to provide a familiar framework for referral sources. Placing information in similar sections with distinct headings allows readers to locate information quickly. Structured report formats also provide a way to organize large amounts of information and to increase efficiency. Table 43-14 depicts important sections that may be included in comprehensive neuropsychological reports and content which may be included in each section.

**TABLE 43-14**  
*Report Structure and Content*

REPORT SECTION	CONTENT OF SECTION
Confidentiality Statement	<ul style="list-style-type: none"> <li>• Include statement indicating that report contents are "strictly confidential" and should not be disseminated or reproduced without the patient's explicit permission</li> </ul>
Agency Contact Information	<ul style="list-style-type: none"> <li>• Include agency name, complete mailing address, telephone number, fax number</li> </ul>
Demographic Information and Referral Source	<ul style="list-style-type: none"> <li>• Include patient's name, address, race, marital status, handedness, date of birth, age, current medications, date of injury, and referral source</li> </ul>
Presenting Problem and Reason for Referral	<ul style="list-style-type: none"> <li>• Highlight presenting problems, including injury date, etiology, and injury specifics</li> <li>• Identify specific referral questions</li> </ul>
Basis of Evaluation	<ul style="list-style-type: none"> <li>• Provide sources of interview information</li> <li>• Identify records which were reviewed</li> <li>• Provide checklist of tests administered in the appendices</li> </ul>
Behavioral Observations	<ul style="list-style-type: none"> <li>• Describe behavioral observations during the testing process, including information presented in Table 43-4 (general behavioral observations included in "Behavioral Observations" section and specific test related behaviors included in "Test Results" section)</li> </ul>
Current Symptoms	<ul style="list-style-type: none"> <li>• Identify current problems reported by the patient and his or her family members</li> <li>• Include current neurobehavioral symptoms endorsed on the Neurobehavioral Functioning Inventory, listing specific items endorsed in a table</li> <li>• Highlight changes in functioning compared to pre-injury</li> </ul>

TABLE 43-14 (continued)

REPORT SECTION	CONTENT OF SECTION
Historical Information	<ul style="list-style-type: none"> <li>• Include information about the following: <ul style="list-style-type: none"> <li>• Academic/vocational history</li> <li>• Family/social history</li> <li>• Medical/mental health history; current treatment</li> <li>• Pre- and post-injury substance use</li> <li>• Criminal history</li> </ul> </li> </ul>
Summary of Medical Records	<ul style="list-style-type: none"> <li>• Provide summary of principal medical and mental health records reviewed</li> </ul>
Daily Living Abilities	<ul style="list-style-type: none"> <li>• Identify current living situation, daily activities, and ability to perform activities independently and safely (e.g., hygiene, driving, medication compliance, financial management)</li> <li>• Note any post-injury change in living situation, daily activities, and independence</li> <li>• Highlight judgment and safety issues, with table depicting responses on the Judgment and safety Screening Inventory</li> </ul>
Test Results	<ul style="list-style-type: none"> <li>• Provide behavioral observations pertaining to approach to testing and reaction to testing</li> <li>• Note level of motivation and effort</li> <li>• Estimate pre-injury abilities (Impaired to High Average)</li> <li>• Describe of test performance in each functional area</li> <li>• Provide table comparing test data to pre-injury estimates, prior tests, and normative data</li> <li>• Provide graphical depictions of selected test results in appendices (e.g., performance across trials on verbal learning tasks, figure depicting MMPI-2 results)</li> </ul>
Impressions	<ul style="list-style-type: none"> <li>• Integrate information from various report sections</li> <li>• Note and discuss consistencies between various information sources</li> <li>• Provide diagnostic formulation and support for each diagnosis</li> <li>• Provide table depicting DSM-IV and ICD diagnoses</li> <li>• Respond to referral questions clearly</li> <li>• Highlight interactions between cognitive, emotional, neurobehavioral, pain, and medical factors</li> <li>• Provide conclusions about prognosis for improvement and future academic and vocational functioning</li> </ul>
Recommendations	<ul style="list-style-type: none"> <li>• Provide practical, feasible recommendations that address cognitive, neurobehavioral, and emotional issues</li> <li>• Provide recommendations regarding judgment, safety, and daily living activities</li> <li>• Provide referrals for services which may improve functioning (e.g., medical follow-up, evaluation, therapy, support group) (see Table 43-9 for sample recommendations)</li> </ul>

## NEUROPSYCHOLOGICAL TREATMENT

Neuropsychologists specialize in the assessment and treatment of neurobehavioral disorders encountered across the lifespan. As treatment providers, neuropsychologists offer invaluable expertise in developing compensatory strategies and identifying resources to help patients cope with disruptions in their daily functioning. Neuropsychological treatments and interventions are ideally created with appreciation of individuals' unique characteristics and needs. Treatment plans aim to accentuate patients'

strengths, to help them overcome neurocognitive and behavioral challenges identified by assessment, and to maximize coping. Staples of neuropsychological rehabilitation include education and referral, individual and family psychotherapy, support groups, behavior management, cognitive remediation, and job advocacy and planning.

### Education and Referral

Research has found that family members of people with TBI most frequently cited health information as an important



need (68). Rehabilitation professionals strive to provide reliable and accurate information about TBI to patients, family members, friends, teachers, employers, and other treatment providers. Bibliotherapy is chosen by many professionals to facilitate communication of vital medical knowledge. Patients may be provided with written material for review and discussion. For example, *Getting Better and Better after Brain Injury: A Guide for Families, Friends, and Caregivers* by Kreuzer and Kolakowsky-Hayner (69) offers pertinent information about consequences of TBI and the recovery process. Rehabilitation specialists may also be called upon to provide referral sources with information about the common manifestations of TBI. Providers of adjunctive therapies are likely to profit from understanding an individual patient's neurobehavioral or cognitive post-injury difficulties.

Patients often demonstrate needs outside the realm of a neuropsychologist's expertise. Treatment providers are encouraged to be mindful of adjunctive treatments which may prove beneficial to patients. Appropriate and timely referrals to alternative treatment professionals are encouraged. The identification of services likely to be helpful to patients is the first step. Rehabilitation professionals may consider patients' abilities and willingness to fully participate and make use of additional treatments. Examples of adjunctive services include substance abuse treatment, psychotropic medication, vocational rehabilitation, clubhouse programs, support groups, or comprehensive driver's evaluation.

### Individual Psychotherapy

Psychotherapy is considered an essential component of holistic treatment for patients with TBI by many rehabilitation professionals (70–73). Qualified neuropsychologists play a vital role in providing psychotherapy for individuals with TBI (71). Individual therapy with patients and family members is a useful and commonly practiced mode of inpatient and outpatient rehabilitation. Patients may benefit from attending sessions without their family members present for private discussions of personal issues. Conversely, family members may be invited to sessions in order to obtain psychoeducation about the patient's injury or to provide input about the patient's functioning outside of session.

Psychotherapy further offers people with TBI the opportunity to learn skills to better deal with dramatic life changes encountered after a TBI. Practitioners and patients with TBI determine mutually acceptable therapy goals to address areas of deficiency. Improving emotional adjustment, communication skills, and symptom management are examples of typical therapy goals. Training in anger or stress management, social skills, and strategies to manage depression or anxiety are therapeutic strategies often employed with patients following a TBI.

### Family and Marital Intervention

Research supports the need for interventions following TBI for families. (68, 74–76). Researchers have found that nine out of 10 patients are discharged to home after inpatient rehabilitation (48). Family members of patients have an understandably difficult time coping with role changes, increased responsibilities, and stress associated with TBI (e.g., insurance issues, financial strain, and medical appointments). Despite the efforts of rehabilitation staff to prepare families for patients' discharge, many family members report feeling overwhelmed and ill-equipped to manage the long-term needs of survivors (18, 77).

Most families do not receive professional emotional support following the TBI of a family member (68). Research on caregiver burden revealed that over one-third of caregivers endorsed clinically significant levels of depression and anxiety (55). Emotional reactions of families following the brain injury of a loved one may also include intense feelings of anger, blame, and guilt. Reassuring family members that these reactions are normal responses to a tragic event can enhance long-term functioning.

Family interventions not only provide a valuable means for improving emotional support, but also may help with symptom reduction and coping skills enhancement. Some family members receive individual therapy as an adjunct to or as a substitution for family therapy. Neuropsychologists are often pro-active in recommending and implementing treatments tailored for the needs of a family or an individual family member.

Psychotherapy provides patients and their families the opportunity to share their feelings of grief, loss, and helplessness in a supportive and understanding environment. Treatment providers also impart information regarding the patients' neurological condition through patient-family education. Information commonly shared with family members includes the effects of brain injury, the process of recovery from TBI, and compensatory strategies. Dysfunction in sexuality may also be addressed as a component of therapy. Psychosocial treatment approaches are associated with helping survivors and their families cope with post-injury issues of such as impaired sexual performance or disinhibition (78). Readers interested in additional information about families of patients with TBI are referred to the chapter in this text by James Malec, Ph.D., "Family and Caregiver Issues and Interventions."

### Support Groups

Support groups for survivors of TBI and their family members or friends provide a number of benefits to participants. Community based support programs offer survivors of brain injury and their family members or friends help in managing a wide range of disability-related stressors. For example, support groups are a source of emotional support, education, and social networking. Participants in a

peer oriented group for survivors reported having increased knowledge about TBI, enhanced quality of life, improved general outlook, and better emotional coping (79). Patients and their families often benefit emotionally from the shared experiences of others. Support group members commonly disclose information regarding resources or coping strategies they have found useful in recovering from TBI. People are given the opportunity to extend their social connections within the community through their participation in support groups. An organization such as the Brain Injury Association of America, Inc. provides referral services and information about local support groups for interested parties. Common objectives of a group for persons with TBI may include discussing needs of survivors and families, sharing information, identifying local resources, and networking. Rehabilitation specialists are encouraged to be familiar with such organizations and groups in their area.

### **Behavior Management**

Behavior management is another tool available to treatment professionals for patients demonstrating disruptive or dangerous behavior. Behavior management may incorporate aspects of cognitive remediation in applying interventions. Behavioral approaches providing emotional support and maintaining sensitivity to the contextual environment of the patient are recommended (80). Yody and colleagues (81) advocate for behavior management training that reduces unwanted behaviors by reinforcing alternative behaviors serving similar functions or purpose. Families and other service providers (e.g., teachers, nursing staff, and employers) may benefit from learning behavior management techniques. Problems such as impulsivity and aggressiveness can greatly interrupt patients' social functioning at work, home, or in treatment facilities. For example, behavior modification techniques to enhance the inhibitory control of patients have demonstrated effectiveness (82).

## **COGNITIVE REMEDIATION**

Ben-Yishay and Diller (83) argued for an integrative, holistic approach to cognitive remediation that considered issues of awareness, self-concept, and self-efficacy. Mateer and colleagues (84) further recommended integrating cognitive and emotional interventions given the interaction between the two domains of functioning. The authors indicated that successful integration maximizes treatment potential.

Direct intervention to address cognitive deficits incurred as a result of a TBI may be obtained through cognitive retraining (85). Neurocognitive domains (e.g., attention/concentration, memory, learning, and planning) and

academic skills may be amenable to remediation efforts. The preponderance of evidence indicates there is some benefit of cognitive rehabilitation programs across a continuum of services (86). Cicerone and colleagues (87) reported that therapies for skill acquisition and domain-specific knowledge could be beneficial for individuals with moderate to severe memory impairments. Research suggests that enhancement of specific skills areas may account for the majority of noted benefits observed from cognitive retraining in such domains as attention (88).

Cognitive rehabilitation typically includes training patients in compensatory strategies to enhance functioning compromised by neurological damage. Patients' strengths and skills are often exploited in attempts to overcome areas of relative neurocognitive weakness. For example, rehabilitation specialists train patients in the effective use of memory logs, checklists, mnemonic devices, and self-monitoring to help them compensate for cognitive deficits. Keith Cicerone, Ph.D., addresses this topic more thoroughly in the chapter entitled "Cognitive Rehabilitation." Table 43-15 depicts programs and strategies developed to ameliorate cognitive dysfunction.

### **Job Advocacy and Planning**

As TBI frequently occurs to young people in arguably the most productive years of their working lives, employment is an especially important issue (111). A common goal for adults who have experienced a TBI is employment or return-to-work (112). Following comprehensive evaluation, neuropsychologists often advocate for services their patients need to successfully return to work. Specific cognitive skills (i.e., concept formation, cognitive flexibility, and problem solving) are cornerstones of functional recovery and successful rehabilitation that may be disrupted by a TBI and identified during the assessment process (111).

Persons recovering from brain injury often require additional programs and supports to supplement traditional models of vocational rehabilitation. Wehman, West, Kregel, Sherron, and Kreutzer (113) conducted a study about the efficacy of a supportive employment program for survivors of severe brain injury. Program participants were matched with a job opening based on preliminary assessments. Interventions such as work and social skills training, job modifications, and counseling were completed. Patients also received assistance with addressing common obstacles to employment (e.g., interpersonal conflicts, or lack of transportation or housing) by an employment specialist. Helping survivors find financially and socially rewarding jobs and appropriate vocational supports enhances the probability patients will experience a successful return to work after a TBI. Wehman and colleagues (114) investigated the long-term follow-up of persons with TBI after being involved in supported employment. Findings suggested that

**TABLE 43-15**  
*Remediation Strategies or Programs Applicable to Various Functional Skill Areas*

FUNCTIONAL SKILLS AREAS	COGNITIVE REMEDIATION	REFERENCES
<b>Academic Skills</b>		
Reading	Phonological & strategy-based	Lovett et al., 2000 (89)
Spelling	Lexical treatment program	Brunsdon et al., 2002 (90)
Arithmetic	Arithmetic problem solving	Delazer, Bodner, & Benke, 1998 (91)
<b>Attention</b>		
	Computer-assisted attention retraining	Gray, Robertson, Pentland, & Anderson, 1992 (92); Wood & Fussey, 1987 (93)
	Attention Process Training	Sohlberg & Mateer, 1987a (94); Park, Proulx, & Towers, 1999 (95)
	Cognitive remediation programme (CRP)	Stevenson et al., 2002 (96)
	Remediation of "working attention"	Cicerone, 2002 (97)
	Virtual reality cognitive training	Cho et al., 2002 (98)
<b>Memory / Learning</b>		
	Prospective memory training	Sohlberg et al., 1992 (99)
	Explicit memory & errorless learning	Wilson et al., 1994 (100)
	Memory strategy training	Yerys et al., 2003 (101)
	Memory book training	Burke, et al., 1994 (102); Sohlberg & Mateer, 1987b (103)
	Electronic memory aids	Van den Broek et al., 2000 (104)
	Structural memory retraining	Ryan & Ruff, 1988 (105)
<b>Planning / Organization</b>		
	Self-instructional training	Cicerone & Wood, 1987 (106)
	Cognitive & metacognitive approaches	Ellis & Lenz, 1990 (107)
	Goal setting, task analysis, and monitoring outcome	Ellis & Friend, 1991 (108)
<b>Problem Solving</b>		
	Problem-solving training	Von Cramon et al., 1991 (109)
	Cognitive-behavioral training	Suzman et al., 1997 (110)

supported employment was cost-effective for individuals with TBI.

The 2005 article by Wehman, Targett, West, and Kregel (115) reviews the research literature with respect to TBI and employment, and provides a series of recommendations for future research and public policy. The reader is referred to the chapter in this book entitled, "Vocational Rehabilitation Issues," by Dr. Paul Wehman for detailed information about employment services for individuals following a TBI.

### SUMMARY

Early on, neuropsychologists were primarily involved in quantifying cognitive abilities and endeavoring to localize brain dysfunction. Over the past several decades many neuropsychologists working in rehabilitation settings have expanded their practice to address the diverse and

long-term needs of persons with brain injury and their families. Neuropsychologists have had important roles on rehabilitation teams addressing issues relating to behavioral management, emotional adjustment, substance abuse, family functioning, and return to work. With larger numbers of people surviving traumatic brain injury, neuropsychologists have had an opportunity to play an increasingly important role in rehabilitation. Undoubtedly, many persons with brain injury face long-term difficulties adjusting and returning to productive lives. Neuropsychologists are often well qualified to help patients and their families, and many have chosen to expand their roles far beyond that of cognitive evaluator.

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# 44

# Principles of Behavioral Analysis and Modification

*Robert L. Karol*

## INTRODUCTION

Psychological considerations are integral to the treatment of persons with brain injury. Most of the elements people use to define their self-worth, such as intelligence, physical prowess, financial status, etc., are vulnerable after brain injury. Moreover, coping skills may decline and behavioral dyscontrol may increase due to alterations in cognition. Treatment protocols that de-emphasize psychological status are less likely to be successful than therapy programs that incorporate psychological deliberations.

Often treatment programs focus on medical, physical, and cognitive factors: (1) walking, balance, transfers between a bed and a chair, or transferring into a car; receptive and expressive language deficits; upper extremity use and activities of daily living; and medical stability. It is natural to give weight to these functions. It is apparent to all professionals when persons with brain injury are unable to walk, talk, or care for themselves. Physicians are trained to intervene when there is medical instability. Moreover, persons with brain injury and their families are exquisitely aware of these problems and they want professionals to fix them. They assume that recovery of personality will accompany physical recovery (2).

Hence, persons with brain injury become a set of symptoms. The term “medicalization” describes this process (3). In part, the power of this process is based

upon our society’s expectation for health care. People in our society expect our health care professionals to act in a certain way – to use medications and high technology to focus on symptom cure – stemming from people’s familiarity with acute medical care, sometimes from media entertainment (4) or from media reporting of advances in research. Professionals accommodate people’s expectations. After all, expectations are an important element in care (5). However, fulfilling this expectation can leave persons with brain injury and their families dissatisfied. Psychological variables determine their comfort level with care, but frequently persons with brain injury and their families articulate poorly their psychological needs. The challenge is that psychological variables seem nebulous and indistinct. Yet, in the long term, factors associated with psychological variables and quality of life can have a greater impact on persons with brain injury and their families than other variables, (6) and cognitive and behavioral concerns tend to be most burdensome (7). To be more helpful, rehabilitation ought to address higher needs related to satisfaction with life (8).

Unfortunately, third party reimbursement sources compound the potential inattention to psychological considerations. Insurance system changes are leading to shorter hospital stays, and there is more pressure on families to provide care at home (9). Nevertheless, insurance often fails to cover community support services (10).



When persons with brain injury are able to walk, talk, perform activities of daily living, and are medically stable, insurers press for program discharge, regardless of whether persons with brain injury or their families are psychologically ready for return to the natural environment, or even for transfer to another program or care setting. Furthermore, there is little attention paid to the willingness to perform skills that professionals have taught persons with brain injury and their families.

It is a mistake when professionals, persons with brain injury, families, and insurers downplay psychological variables. Psychosocial sequelae may be a better predictor of outcome than physical symptoms (11). Also, outcome itself can be a function of psychological care. The intensity of psychological care correlates with cognitive gains (12). Hopefully, this is familiar knowledge among rehabilitation professionals. Behavioral or emotional dysfunction can be hard to treat and untreated can disrupt the care of cognitive and physical functioning (13). The satisfaction persons with brain injury and their families express regarding their rehabilitation is likely to be influenced by their perceptions of their treatment. Awareness of the importance of psychological variables is important. Sadly, families report being inadequately informed about brain injury and rate professionals as unhelpful (14).

Hence, this chapter will address behavioral and psychological care. The intent of the chapter is to provide an overview of assessment and intervention methods and issues, identify important behavioral and psychological process variables in rehabilitation, and highlight selected applications.

## PRINCIPLES OF ASSESSMENT AND INTERVENTION

### Assessment

*Introduction to Assessment* Professionals ought to predicate treatment on thorough assessment. Psychological assessment dovetails with evaluations by all other disciplines because psychological variables affect the outcome of all disciplines' evaluations and their treatment efforts. For example, low effort due to depression can contaminate the findings of physical therapists. Hopelessness can interfere with the educational efforts of nurses leading to poor reliability in the self-administration of medications. The beliefs of persons with brain injury influence compliance with physicians' recommendations. Therefore, psychological assessment is essential for the provision of services to persons with brain injury, not just for psychological care, but also for success by all disciplines.

Psychological assessment primarily covers three domains: emotional, behavioral, and cognitive functioning. Emotional status includes factors such as depression,

anger, anxiety, etc. The examples in the preceding paragraph derive from emotional variables that have behavioral implications. Behavioral considerations range from noncompliance to aggression. Cognitive functioning includes executive processes, memory and learning, intellectual abilities, etc. and are evaluated using clinical observation and neuropsychological testing.

*Assessment of Emotional Status* Emotional disturbance is a significant component of brain injury. The National Institute of Health Consensus Statement (15) states, "Mood disorders, personality changes, altered emotional control, depression, and anxiety are also prevalent after TBI" (p. 12). Because the brain regulates emotional functioning, (16–18) organic damage can cause direct emotional changes. In addition, the recognition and expression of emotions can be altered by brain lesions (19). There is also the emotional adjustment to having and living with a disability. There have been numerous reports of the emotional sequelae of brain injury (11, 20–22). Recently, researchers have also paid particular attention to grief as distinct from depression (23).

Professionals can use clinical acumen and psychometric assessment to determine emotional functioning. They should decide how to balance these two approaches based upon the setting and the level of functioning of the persons with brain injury with whom they are working. For instance, in a community-based setting with higher-functioning individuals, psychometric evaluation may be feasible, but at Rancho Los Amigos Level V (24) it is untenable with people newly arrived from an intensive care unit fresh out of coma.

Clinical assessment of emotional functioning occurs through a combination of diagnostic interview and observation. Interview can provide clues as to what persons with brain injury are experiencing. How persons with brain injury express emotions can provide insight into their coping abilities. Of course, professionals need to be aware of deficits in the expression of emotion, such as aprosodia (the loss of speech tone that conveys affective data), that might mislead professionals in their judgment regarding emotional status. Observation when persons with brain injury demonstrate emotional dyscontrol provides clues as to what they are feeling. Fluctuations in emotional intensity throughout the day, from day to day, or across events offer professionals the opportunity to study emotional patterns. Professionals must observe the antecedents and the consequences of emotions as well as the qualitative and quantitative aspects of the emotions to fully understand the expression of emotions. Experienced professionals, for example, might determine upon close observation that a diagnosis in the chart of depression is, in fact, anxiety. Trained observation of emotional events is often worth much more than only obtaining professionals' reports or reading the record. A combination of

interview, providing leads in regard to emotional status, and observation of emotions in practice during behavioral events can assist professionals in the exact delineation of emotional functioning.

In the case of psychometric assessment, there is an unending array of published psychological test instruments for the determination of emotional functioning. These range from measures of particular emotional variables (e.g., Beck Depression Inventory) (25, 26) to broad personality inventories (e.g., MMPI). There are also rating scales, questionnaires, and interview formats that include emotional or adjustment variables (e.g., Neurobehavioral Rating Scale-Revised, (27, 28) Functional Assessment Measure, (29–31) Mayo-Portland Adaptability Inventory (32–34)). Interview, observation, or both ought to accompany any psychometric assessment of emotional variables. Qualitative variables can be crucial in emotional assessment: how persons with brain injury experience or express emotions provides insight into their functioning beyond psychometric tools.

Professionals must consider the appropriateness of any instrument for the evaluation of emotional status for persons with brain injury. First, it is helpful when there are norms for persons with brain injury for the particular instrument. While it is important to be able to determine if persons with brain injury deviate from the general population, it is also useful for rehabilitation to know if they diverge from the normal experiences of other persons with brain injury. Publishers of standardized, mass-marketed tests of emotional adjustment generally fail to include a subgroup of persons with brain injury during test development. Furthermore, when they include persons with brain injury in a sample, the subject characteristics in any particular study of the brain injury population may differ in some significant fashion from the persons with brain injury being seen by a given professional. Important distinctions may exist on variables including the nature of onset, location of damage, time post onset, pre-morbid personality dimensions, etc.

Second, cultural variables can play a critical role in the psychometric assessment of adjustment after brain injury. Professionals may be aware of the impact of cultural factors on personality assessment in mental health populations, but they are potentially less in tune to the intersection of culture and coping with disturbances in physical health, particularly various cultures' differing views on appropriate approaches to brain injury. Behaviors that may appear pathological in one culture may represent normative beliefs in another culture (35). In light of the alterations in personality and cognitive functioning that can occur after brain injury, people have a complex emotional response to brain injury symptoms based on their social and cultural views of the symptoms.

Third, the neurological experiences of persons with brain injury are unique contaminants to the assessment

of emotional status. Many markers of emotional states in mental health populations include neurological or physiological functioning (e.g., impaired concentration or memory, sleep disturbances, alterations in initiation or energy level). However, for many persons with brain injuries these are normal reflections of organic impairment and may be unrelated to emotional disturbance. There have been investigations of the impact of such factors on emotional assessment, for example for depression, and the effect of these variables varies (36–38).

Yet, many persons with brain injury have had experiences that would indicate clear emotional pathology in mental health populations. When persons with brain injury report histories of periods of “blacking out” or “out of body episodes,” they could be due to coma or seizures; reports of hallucinations may be recollections of emergence from coma; acknowledgment of “delusional thoughts” could be confabulations during rehabilitation. While it is certainly possible that persons with brain injury have had blackouts, out of body episodes, delusions, hallucinations, etc. as a function of emotional pathology, the attribution of these symptoms ought to include the differential diagnosis of normal brain injury sequelae. Professionals must adjust their interpretations of psychometric instruments that utilize symptoms commonly occurring after organic brain injury.

Self report by persons with brain injury can also be a concern due to the injury. Memory deficits, in particular, can be a barrier to psychometric assessment of coping. When a test requires recall of personality based preferences, coping styles, past emotional experiences, or previous behavioral episodes, persons with brain injury may not be able to remember what they have done or what type of people they were in the past. It is common for persons with brain injury to relate that they are unable to remember how they were feeling at a particular point in time. Sometimes denial or lack of awareness can have a global effect on self report measures. A person with brain injury might self report an emotional picture that substantially conflicts with the one that professionals would obtain from significant others about their loved one with the injury (e.g., a person with brain injury might fail to report depression that is clearly present to other observers). Since many tests rely on self-reported recall of preferences, emotions, and behaviors, professionals must be cautious in the interpretation of psychometric test results of adjustment and coping styles for some persons with brain injury.

Finally, professionals must take care in the actual administration of psychometric tests of adjustment to persons with brain injury. Cognitive deficits can impair the ability of persons with brain injury to complete the tests or they can lead professionals to misinterpret the results because the findings are affected by cognitive deficits during test administration. Reading ability is one obvious

determinant for the suitability of a test. Other factors range from concentration (partial attention paid to test items as well as variable effort in completing the test) to comprehension and aphasia (understanding the directions and the test items) to even visual-perceptual ability (for visual analog or Likert scale measures). Even difficulty with decision making can interfere with responding to test items.

*Assessment of Behavior* It is essential that professionals formulate any intervention program for behavioral problems on sound behavioral assessment. The principles of behavioral analysis and assessment are well-established (39–41). Furthermore, their application to brain injury care has been detailed for some time (42, 43). Behavioral assessment routinely begins with decisions about which behaviors to assess. This is crucial. If professionals fail to appreciate the nature of their raw observations before measurement, they will operationalize and measure the wrong events or the unimportant aspects of events. Good clinical judgment must precede behavioral measurement. Next, behavioral assessment entails professionals defining in operational terms the behaviors they select. They then can observe behaviors and record frequency, severity, duration, etc.

Standardized rating of behavior is an alternative to individualized assessment of operationally defined target behaviors unique for each person. In this approach, behaviors such as aggression, noncompliance, or irritability are rated using predefined definitions of behaviors. Ratings can be completed by professionals, families, persons with brain injury, or someone else. The Agitated Behavior Scale (44) is an example of a rating scale with items covering impulsivity, violence, wandering, etc., as is the Neurobehavioral Rating Scale (45) with items including disinhibition, agitation, hostility/uncooperativeness, etc.

Regardless of the approach, two hurdles loom large related to the nature of behavioral dyscontrol after brain injury. First, the behaviors that most concern professionals, families, and others after brain injury are exceedingly complex. The process of defining behaviors in operational terms takes considerably more time and effort than many professionals anticipate. Second, overly simple behavioral assessment that involves just recording easily correctable aspects of behavior will miss important antecedents and qualitative variables that provide clues to treatment. This is especially so in light of cognitive and emotional impairments after brain injury that complicate behavioral etiology. Unfortunately, professionals in rehabilitation settings often approach record keeping for behavioral problems with ambivalence (46). The combination of needing excellent assessment, with the difficulty of knowing what to assess, and professionals' challenges in implementing assessment procedures can defeat efforts at treatment.

*Assessment of Cognition* A keystone for successful behavioral treatment of persons with brain injury is evaluation

of their cognitive functioning. Cognitive disturbance has far reaching implications. It affects emotional coping, behavioral dyscontrol, participation in physical and medical care, and return to independence and productivity. The foundation of cognitive assessment is neuropsychological evaluation. Neuropsychological evaluations are addressed in the chapter by Drs. Taylor, Livingston, and Kreutzer; however, there are two aspects of cognitive evaluations that are particularly pertinent to the current discussion.

The first aspect is the utilization of neuropsychological information to help formulate the treatment of emotional issues and behavioral dysfunction (47). Neuropsychological data greatly facilitates the treatment of emotional and behavioral problems, (48) though care must be taken to not rely solely on neuropsychological data (49). Still, many emotional and behavioral problems are partially based upon cognitive difficulties. For example, paranoia can be a reflection, in part, of attentional and memory deficits when persons with brain injury have perceptions of other people that are inaccurate because of a failure to attend to and recall all of the elements of an interaction. Similarly, speed of processing deficits can cause anger outbursts when persons with brain injury are unable to keep up in conversations, leading to frustration with getting their needs heard. Any study of behavioral dyscontrol or emotional distress ought to include cognitive processing assessment.

Second, professionals need to realize the importance of clinical observation for the determination of cognitive deficits. Sometimes issues of injury severity or non-cooperation render formal neuropsychological testing impractical, forcing professionals to rely solely on observation of cognition, while at other times observation of cognitive deficits is a crucial adjunct to testing. Experienced professionals should watch an emotional or behavioral event with an eye towards noticing how cognitive deficits influence the timing, severity, and nature of the event, as well as the effect of cognitive deficits on coping strategies. Also, observation of the impact cognition has on emotion and behavior provides excellent hypotheses for neuropsychological testing. The converse is also true: neuropsychological data can help refine professionals' observations, making the time spent on observation more productive.

## Intervention

*Contingency Management* The rubric contingency management, in brief, refers to the application of reinforcement and punishment to alter and control behavior. The principles of contingency management are well delineated, (40, 50) and professionals traditionally use these procedures for the treatment of behavioral dyscontrol after brain injury. It behooves professionals, however, to be certain that they correctly apply these procedures.

Many professionals across disciplines who attempt to utilize contingencies assume that they are simply to apply, whereas, in fact, they are quite complicated.

Technically, a reward is something that increases a behavior and a punishment is something that decreases a behavior. Professionals can explore a wide range of rewards and punishments (e.g., social, tangible, tokens/points) (51). Unfortunately, sometimes professionals independently believe something is a reward or a punishment and then apply it to change the behaviors of a particular person. This is problematic because the consequence may not be a reward or a punishment for that individual. Professionals should observe behaviors and discuss rewards or punishments with the person before plan implementation. It can be helpful to use access to naturally occurring behavior as a reward for the performance of lower probability behaviors that professionals want to encourage (52).

A positive reinforcer, when *presented*, increases a behavior; a negative reinforcer, when *removed*, increases a behavior. Many professionals often misunderstand the latter: negative reinforcement is not punishment! Both positive and negative reinforcement are rewarding. Punishment also can occur in two ways: the *application* of something unpleasant (positive punishment) or the *removal* of something pleasant (negative punishment) (52). Both forms of punishment decrease behavior. Table 44-1 summarizes the relationship between reinforcement and punishment, with examples.

Punishment is frequently misapplied. Punishment will not increase a desired behavior. Professionals cannot teach correct behavior with punishment. Moreover, punishment typically suppresses a behavior, but can be impermanent: when the punishment stops, the behavior may return (40). Also, as punishment begins behavior may

worsen. There may be significant emotional responses and punishment may lead to aggression (39, 52). If professionals endure the period of worse behavior, persistent application of punishment may eventually suppress behavior. However, the severity of aggression or other behaviors that adults with brain injury can produce in response to punishment is usually beyond what most professionals or programs are willing to tolerate.

Punishment can be detrimental to the process of treatment. It can impair rapport. Professionals may find that those persons to whom they are administering punishment avoid them (39). At the same time, however, persons with brain injury receiving punishment may learn from professionals to use punishment to change the behavior of other people. Professionals who provide punishment may be seen as models for how to act (52).

Punishment carries with it numerous significant ethical and moral concerns, beyond its ineffectiveness in teaching adaptive compensation strategies. In addition, there are regulatory standards regarding the use of aversive or psychologically risky procedures (53). Skilled professionals generally advise against the use of punishment (54). It is unnecessary, and it is fraught with risk for misuse. Still, punishment requires discussion because professionals working with persons with brain injury can slip into punitive paradigms. Punishment can even be reinforcing for professionals because it may rapidly decrease unwanted behaviors (52). Punitive acts may include discharge from rehabilitation by overwhelmed professionals who label persons with brain injury as dishonest or unmotivated (55).

In contrast, professionals can utilize reinforcement to teach appropriate behavior because it works to increase behaviors. However, the pattern of reinforcement influences how subsequent behavior occurs. There are four primary schedules of reinforcement. The first one is “fixed ratio:” the frequency of responses required to achieve reinforcement is set, and reinforcement occurs based on that frequency (e.g., every fourth time). This schedule encourages fast bursts of responding because the faster people perform, the more reinforcement they receive. However, there tend to be behavioral pauses after reinforcement. Typically, reinforcement is given every time (continual reinforcement) at the start of treatment and faded over time to a less frequent rate (intermittent reinforcement).

The second schedule of intermittent reinforcement is called “variable ratio.” Professionals provide reinforcement on a schedule with an average frequency of required responses (e.g., on average every fourth time), but with random variation around the average. This produces a higher rate of responding with more uniformity than fixed ratio schedules.

The third intermittent schedule is “fixed interval.” In this schedule, reinforcement happens after a set interval

**TABLE 44-1**  
*Positive and Negative Reinforcement and Punishment*

TYPE	ACTION	
	PROVIDE	REMOVE
<b>Desirable</b>	<i>Positive Reinforcement</i> Increases behavior (Salary at work)	<i>Negative Punishment</i> Decreases behavior (Revoking driver's license)
<b>Undesirable</b>	<i>Positive Punishment</i> Decreases behavior (Spanking)	<i>Negative Reinforcement</i> Increases behavior (Potential early prison parole)

of time. This schedule can cause a “scallop” effect in which appropriate behavior increases as the time for reinforcement approaches and then declines after reinforcement.

The fourth intermittent schedule is known as “variable interval.” Variable interval schedules eliminate the scallop effect because reinforcement happens after the passage of an average amount of time, not a consistent, set amount of time. Learning with variable intervals of reinforcement is fairly resistant to extinction (the cessation of a desired behavior during periods of a lack of reinforcement). Variable interval schedules produce a more uniform response than fixed interval schedules.

It can be difficult for professionals who are unfamiliar with reinforcement schedules to keep in mind the various options. Table 44-2 provides familiar examples of the four basic schedules of reinforcement to help identify them. Of course, there are other schedules of reinforcement and professionals may even form schedules including conjunctive schedules that require adherence to two or more performance requirements to receive reinforcement or they may chain different schedules together (52). The variations are countless.

Professionals must carefully examine how they deliver reinforcement compared to how they intend to provide it. There must be consistency in reinforcement across all professionals. Problems surface when a single professional is inconsistent or there is variability among many professionals. When one professional is inconsistent, treatment effectiveness will decline and may induce confusion or anger from persons with brain injury. If some professionals provide reinforcement, but other professionals do not, staff-splitting by persons with brain injury will likely ensue. Similarly, professionals may be pitted against family members, for example, when one group reinforces or extinguishes behaviors and the other set does not. Reinforcement will fail when there is inconsistency across professionals or between professionals and families.

Professionals must also be certain that the way a team of professionals reinforces behavior matches the treatment plans. For example, suppose a person with brain injury is to be encouraged whenever the person attempts a particular desirable behavior or coping strategy

(fixed ratio/continual reinforcement). Instead, busy or unaware professionals provide encouragement at the end of their workday in the late afternoon for efforts during that shift (fixed interval). Chart entries note better behavior in the afternoon with gradual improvement as time passes (scallop effect). This is occurring because of the inadvertent change in the schedule of reinforcement.

Consistency with plans is essential when using reinforcement. Furthermore, social attention (positive reinforcement) in response to maladaptive behavior (e.g., aggression) or escape from unwanted activities (negative reinforcement) such as difficult rehabilitation treatment due to behavioral dyscontrol (e.g., noncompliance) can unintentionally maintain undesirable behaviors (56).

The use of reinforcement is more complicated than just deciding on reinforcement schedules. A behavior must first occur for professionals to reinforce it. Professionals can prompt behaviors using cues and instruction so as to initiate behaviors; once behaviors have begun, professionals can reinforce them. Thereafter, professionals can gradually discontinue the prompts. Also, desirable behaviors may begin in rudimentary forms. Professionals must shape the behavior by reinforcing successive approximations of the behavior, progressively requiring more sophisticated approximations of the final behavior before reinforcement occurs. Professionals can also chain behaviors together.

Generalization occurs when behaviors that one learns in a particular setting occur in other settings, even without reinforcement of the behaviors in the new setting. Of course, professionals can encourage generalization with prompting and initial reinforcement. Professionals may also observe response generalization of the behavior to similar behaviors: learning a behavior influences the frequency of similar behaviors. This can be quite beneficial. For example, increased willingness to take showers may generalize to increased room cleaning.

Extinction is an additional tool. When professionals fail to provide reinforcement following behaviors they are using an extinction paradigm. When professionals ignore an emotional outburst on the part of a person with brain injury, they are extinguishing the behavior. As powerful as extinction can be, professionals must appreciate crucial factors in its use. Often, after extinction begins, there is a surge in the behavior. If the behavior is dangerous (e.g., aggression or self-injurious behaviors), the burst of behavior carries increased risk. There may also be periods of spontaneous recovery: after the behavior declines or stops, it may temporarily reappear. Professionals must take care to avoid unintentionally reinforcing either a burst or spontaneous recovery of the behavior. It is important to note that the schedules of reinforcement under which behaviors were acquired influences their resistance to extinction. Finally, extinction is best paired with reinforcement of alternative behaviors.

**TABLE 44-2**  
*Examples of Reinforcement Schedules*

SCHEDULE	EXAMPLE
Fixed Interval	Weekly paycheck
Variable Interval	Good performance on pop quizzes
Fixed Ratio	Factory piecework
Variable Ratio	Slot machine payouts

Behaviors often must be situation specific. As well as learning what to do, persons with brain injury must learn where and when to act. Professionals must reinforce behaviors in certain settings and not in others, teaching when and where behaviors ought to occur. Persons with brain injury often need instruction in reading social cues and context. Otherwise, they may do behaviors appropriate for home, for example, in other settings or they may attempt conversations acceptable with intimate friends when they are with strangers.

Professionals can use contingencies selectively. There are at least four useful procedures: differential reinforcement of other behavior (DRO), differential reinforcement of incompatible behavior (DRI), differential reinforcement of alternative behavior (DRA), and differential reinforcement of low-rate behavior (DRL) (57). In DRO, professionals provide reinforcement when an identified undesirable behavior does not occur. Using DRI, professionals reinforce a behavior that interferes with or prohibits an undesirable behavior. For DRA, reinforcement happens for a desirable behavior while ignoring an unwanted behavior. Lastly, in DRL, reinforcement occurs in response to the reduction of an unwanted behavior.

Token economies are a special format for the implementation of contingency management treatment. In token economies, professionals establish explicit rules for the delivery, withholding, or debiting of tokens (or some other accounting system, such as points) based upon the performance or absence of behaviors that professionals delineate. These tokens can be exchanged by persons with brain injury for reinforcing items, activities, etc. that professionals specify. In essence, the tokens substitute for money in a real economy (41). Tokens serve as conditioned (or secondary) generalized reinforcers (41, 52). They are conditioned or secondary in that people learn to associate them with things that are reinforcing (i.e., tokens by themselves have little inherent value without a relationship to what one can exchange for them). They are generalized because one can exchange them for several sources of reinforcement. Of course, unlike money, tokens can only be redeemed within the closed token economy of defined rewards.

Token economies have a number of advantages over simpler contingency management efforts (40). There may be less satiation than would occur with a set reward because a variety of reinforcers may be purchased with the tokens. For persons with brain injury this can also provide a sense of choice. They may choose diverse rewards or settle on particularly desirable ones. The flexibility may help persons with brain injury feel engagement with the process of behavioral change, though professionals should similarly involve persons with brain injury in the selection of reinforcers in even simpler contingency management plans.

Since persons with brain injury can accumulate tokens toward a valuable or large reinforcer, professionals can use them to permit a measured acquisition of a valuable reinforcer. A corollary of this is the specification that a person can choose to save tokens, as permitted by the economy rules, or to spend the tokens shortly after they earn them. Still, tokens can prove to be strong reinforcers because of their power to translate into significant rewards. Also, tokens can decrease the delay between behavior and reinforcement because professionals can provide them expeditiously. Rather than disrupting the flow of behavior by immediately giving a reinforcing item or event, professionals can easily provide tokens. Professionals must take care, however, in that tokens can become a stimulus for when to perform well and behavior may be different when they are not available (40).

Professionals must recognize that in many ways they are administering an *actual* economy. In the real economy people sometimes under perform and expect to be paid, use legalistic arguments regarding precise procedural concerns to reduce debits for improper behavior (e.g., financial penalties for crime), seek ambiguities in the specification of permissible behavior (e.g., analysis of tax code loopholes) to retain more money, commit theft to increase funds, hide inappropriate behavior, blame other people for their own acts, etc. In a token economy, persons with brain injury may also attempt to outfox the rules through procedural challenges, loopholes, theft, hiding behavior, blaming others, etc. For example, they may seek tokens for behaviors close to those behaviors that professionals specify as due reinforcement or they may claim that certain behaviors do not warrant a debit because the behaviors are not exactly the behaviors listed in the token economy behavioral descriptions (e.g., touching someone's hair does not count as touching the *person* or standing three inches away from someone does not count as *touching* them).

Professionals must consider devoting extra time to the design and implementation of token economies. Token economies can be intrusive in care environments and they can be cumbersome (39). Professionals must delineate each behavior. They must carefully codify in detail what they will use as tokens, how much each behavior earns or costs, how many earned tokens can accumulate, what reinforcers tokens can purchase, how tokens will be exchanged for reinforcers, how the token economy will terminate, etc (39). Obsessiveness helps. However, once in place token economies can provide professionals with a structure to address behavioral dyscontrol (58) and can be used across disciplines (59).

Token economies can be helpful for behavioral issues arising from brain injury. Professionals can implement a token economy with a single person with a brain injury (60) or in a programmatic fashion (61). However, as with any treatment, professionals must individualize treatment.

The use of any contingency management procedure is complex. There is no practical cookbook to guide professionals about which procedure to utilize with which symptom or person. Since treatment must be founded on individual, multifaceted symptom patterns and causes, any pre-determined treatment algorithms will fail to capture the extraordinary diversity of clinical presentations and etiological variables upon which professionals should base treatment. Moreover, as has been reviewed in the preceding discussion, contingency management encompasses a breadth of actual procedures that are highly intricate. Still, contingency management is likely to work best when three conditions are met.

First, they are more effective when persons with brain injury accept the idea of explicitly receiving reinforcement from another adult to alter their behavior. Not surprisingly, many persons with brain injury reject the idea that professionals are intentionally reinforcing their behavior. They dislike the manipulative feeling that apparent contingency procedures engender. While adults may use consequences to alter the behavior of children, adults in our society resist the idea that other people may attempt to apply contingencies to their own behavior. Persons with brain injury feel similar in this regard to any other adult and may resist contingency paradigms that remind them of being treated by professionals as if they are children whose behavior is to be controlled by others. Certainly, using contingencies with persons with brain injury who are suspicious or paranoid is contraindicated (62).

Second, when persons with brain injury act in their own best interests contingency management is more effective. Some persons with brain injury fail to do so because of their cognitive impairments, even when they understand and recall the likely consequences. Despite their awareness, factors such as lability, rigidity, nonverbal processing deficits, impulsivity, and executive dysfunctions lead to the failure of consequences to change behavior. Persons with brain injury may strike someone and later acknowledge having had awareness of the consequences, but they still proceeded. These persons may report either they could not stop themselves or could not think about the consequences quick enough to change their behavior. Sometimes they will state that the need for emotional release overrode their reflections about consequences.

Third, contingency management is likely to be more useful when memory difficulties do not interfere. Professionals must consider the impact of memory deficits on the effectiveness of contingency procedures. Many persons with brain injury forget their own behavior before professionals have an opportunity to respond with consequences. This defeats the purpose of linking behavior with consequences. Some persons with brain injury, when they are in a situation where they might choose a behavior that professionals have previously reinforced, forget the previous event. Because they forget that there were

consequences last time, the previous consequences have no influence. Both of these scenarios can defeat the use of consequences. However, there is evidence that in younger persons with brain injury consequences can work even when there exists impairment in explicit memory (memory of consciously recalled information) (63). Still, consequence-oriented behavior management outside of controlled environments can be relatively ineffective (64).

*Errorless Learning in Intervention* The errors people make at the start of learning are an additional concern in the use of contingency techniques. There are potential cognitive (e.g., interference with acquisition) and emotional (e.g., frustration, self-esteem) issues that arise with persistent errors. In contrast, errorless learning provides structure and cues, with initial performance demands set at an achievable level, so that as task complexity increases persons with brain injury perform correctly at each step. Correct responses can be provided to insure avoidance of errors. When applied to cognitive learning tasks, there is evidence of the benefit of errorless learning procedures (65–67). Professionals can apply errorless learning procedures to behavioral concerns (68). In doing so professionals insure that the situations persons with brain injury confront are of a type and level of complexity they can handle, with adequate prompts and training, before proceeding to more difficult emotional and behavioral challenges. Comprehensive programs can be built around errorless learning that adopt a holistic approach (69). Of course, contingency techniques, including reinforcement, stimulus fading, and cueing, can be incorporated into errorless protocols.

*The Impact of Modeling on Intervention* People receive vicarious reinforcement from observing other people receiving contingencies (70). Therefore, persons with brain injury may benefit from their observations of other people receiving reinforcement. If they see other people obtaining desirable consequences for certain actions, they may imitate the same behavior in anticipation of obtaining the same results. Moreover, they may determine that certain behaviors are socially acceptable upon observing the results of those behaviors. Professionals must take care, therefore, that they publicly encourage only behaviors that they wish to have emulated.

There are two issues, in particular, that professionals have to attend to regarding modeling. First, in some instances, professionals will reward one person with a brain injury for a particular behavior when doing so is part of the treatment plan, but not the same behavior from another person. Suppose professionals award a particular reward to someone who achieves a relatively low behavioral milestone, but one that is difficult for that person to reach. A much higher level functioning person with brain injury, who has loftier goals, observes this.

The second person, who is capable of much better behavior, demands rewards for behaviors similar to those of the first person, despite that behavior being well below the second person's capabilities. Individualized treatment plans based upon ability and goals are essential, but professionals must be astute in their application of the plans so that they avoid cross contamination.

Second, professionals must be cognizant of the modeling effect of their own behavior (46). Professionals are being watched: persons with brain injury notice professionals' behavior. For example, professionals may have difficulty teaching physical boundaries when persons with brain injury observe them patting each other on the back; professionals who are heard telling each other off-color jokes may struggle to teach sound sexually appropriate behavior; professionals who make an offhand comment about another professional contribute to staff-splitting and noncompliance by persons with brain injury. There are no off-the-record statements, attitudes, or behaviors on the part of professionals if they can be observed, detected, or implied by the persons with brain injury whom they serve. Professionals must constantly be attentive to the powerful impact of modeling.

Of course, modeling can also be a very powerful positive influence. Professionals can model appropriate behavior, emotions, and skills. Modeling can range from specific skills to more pervasive attitudes. Appropriate modeling can accelerate learning (71).

*Environmental Intervention* Environmental change strives to influence behavior by alteration of antecedent conditions. In general, how other people act toward persons with brain injury and physical elements in the environment comprise the antecedent conditions. Of the two, how other people act is probably the more crucial. In one estimate, 95% of maladaptive behaviors were felt to be a function of how professionals acted (72).

Environmental control emphasizes the establishment of environments conducive to appropriate behavior. The correct environment will vary for persons with brain injury depending upon their cognitive and emotional functioning. Ideally, professionals' attention to neuropsychological and psychosocial factors will permit the creation of a "Neuropsychosocial Environment," (48) one based on the etiological "phenomenology of dyscontrol" of each person. In "Neuropsychosocial Intervention" all of the elements that contribute to the occurrence of behaviors constitute the phenomenology of dyscontrol, including the obvious — cognition and emotions; the discoverable — self image, values, family influences, expectations, pre-morbid personality; and the subtle — noise tolerance, privacy needs, responses to others' appearance, sleep cycle effects, professionals' attitudes, etc. Once professionals comprehensively consider all of the factors that determine the occurrence of each behavior, they can

formulate the neuropsychosocial environment, a psychological and physical world, for each person that obviates the need for undesirable behaviors or interferes with their occurrence. The goal is to create a world consisting of the behaviors of others and physical plant elements that matches the capabilities of each person (48). In essence, persons with brain injury encounter only situations they can handle.

An environmental approach can address severe behaviors. However, there are two challenges: the need for careful observation and generalization (73). Systematic observational assessment is necessary to precisely determine the antecedent conditions leading to behavioral dyscontrol. Professionals must decipher the exact behavioral triggers in a complex social world for persons with impairment in cognitive and emotional functioning. Second, since the approach is not skill building, but environmental engineering, generalization can be a concern. Professionals must therefore strive for changes that are effective, transferable to additional settings, and doable by core people constituting the natural environment.

Environmental change is useful on its own or as an adjunct to other treatment. For example, it can be beneficial until skill building can take place (68). Positive behavioral supports (64, 74) designed to organize antecedent conditions combine skill building with environmental structuring. Moreover, professionals can arrange specific environments that match the abilities of persons with brain injury and then modify them as they can tolerate changes (75). Finally, professionals can use environmental control early in recovery as persons with brain injury emerge from coma (76).

In general, an environmental approach is proactive (before an episode of behavioral dyscontrol happens) in contrast to contingency management, which is reactive (after behavior occurs). Persons with brain injury encounter a positive world, one they can handle, individualized for each person. This creates a framework for success. One notable effect of an environmental approach is that treatment plans describe how professionals should act before behavioral dyscontrol occurs, not merely how they should act afterwards (74).

*Counseling and Intervention* Psychotherapy is an information exchange. Professionals convey ideas or, at least, encourage certain ideas. With new information, or enhanced awareness of previously known information, persons with brain injury, or anyone else in counseling for that matter, gain insight and skills. The usual intent is to influence emotion and behavior, although sometimes experiences during counseling sessions can be beneficial emotional events.

For many persons with brain injury the insights and skills they learn through counseling are invaluable. After all, most persons with brain injury arrive at their injury



with little or no knowledge of what to expect. They are often afraid and worried. It is very difficult to cope and adjust without knowledge, and they must do so with a brain that is impaired in its information processing skills.

There are a myriad of issues that persons with brain injury must face. These concerns begin in the acute rehabilitation center. Professionals need to be aware of how persons with brain injury perceive rehabilitation. From the professionals' perspective, rehabilitation professionals are the "good guys," there to help people who are critically injured become healthy enough to leave the hospital with the skills and knowledge to thrive. In fact, excellent rehabilitation centers seek to help persons with brain injury achieve goals that they have set for themselves to reintegrate into society.

From the perspective of persons with brain injury, there may be a very different reality. The rehabilitation center can be an unfamiliar, busy place with procedures and rules that are implicit, not explicit, or confusing. Persons with brain injury can feel uncertain in the rehabilitation center, not just because of their lack of experience with the physical space, but because of inexperience with the operational characteristics of rehabilitation: roles, schedules, regulations, procedures, and culture. Treatment environments following brain injury are alien places to most people (77). Also, professionals are strangers and therefore, at least initially, are untested sources of reassurance.

Persons with brain injury can struggle early with their sense of loss of control. Professionals must appreciate how hard it is for persons with brain injury to cope with the imposition of rules and schedules for sleep, nursing care, meals, therapies, and visits from family or friends. Even when professionals provide choices, the professionals set the parameters for the decision-making. Professionals assign the label "non-compliant" to persons with brain injury who fail to adhere to the choices that professionals permit.

Counseling can assist persons with brain injury to adapt to the rehabilitation experience. Early reassurance regarding how the rehabilitation team functions is essential. Counseling can provide rationales for professionals' decisions and place them within the context of recovery. It can also address issues of self-esteem that arise when formerly independent adults find themselves dependent on other people who make decisions about them.

Alternatively, counseling can assist persons with brain injury to learn to assert their desires in an effective manner. Professionals traditionally conduct rehabilitation with assumptions about processes, values, and goals that persons with brain injury might not share. Counseling can help bridge paradigm mismatches that would otherwise lead to conflicts between persons with brain injury and professionals. It can help persons with brain injury to delineate their perspectives with the intent of influencing

how rehabilitation professionals provide services to them and what services they want.

Counseling should continue after discontinuation of acute rehabilitation. Major life issues that professionals ought to have broached during rehabilitation typically come to the forefront of attention after hospitalization. Being confronted by the reality of a situation is emotionally different than preparatory, theoretical discussions. Issues that loom large usually include interpersonal relationships, work, driving, finances, sexuality, chemical use, supervision, and living arrangements. Some of the most important counseling happens after acute rehabilitation.

Professionals who provide counseling can face a difficult situation when persons with brain injury confront these issues. Many persons with brain injury want to assert themselves by returning to previous activities. In part, the role of professionals should be to help fulfill this desire when possible, but when persons with brain injury have limitations that require them to adapt to alterations in lifestyle or when society will not adjust to their strengths and weaknesses, it can fall upon professionals to facilitate awareness and coping. This is a complex challenge. Poor awareness is a highly complex symptom often with multiple aspects and determinants; (78–83) its treatment can be exceedingly difficult. Professionals must learn to be the voice of insight and, simultaneously, the source of support.

It is crucial that professionals build rapport with persons with brain injury before helping them confront reality. An empathetic treatment ambiance is essential when counseling persons with brain injury (84). Trust is essential to help persons with brain injury through the rapids of life. However, professionals should prepare for persons with brain injury to reach the point in time when they no longer want guidance. Many persons with brain injury want to strike out on their own, trying out their own ideas and abilities. Professionals must know when to prohibit plans and when to permit trial and error learning. Dangerous plans require professionals' prohibitions. For example, professionals should intervene when someone lacking the required skills intends to drive or return to a dangerous job, such as welding. On the other hand, even if neuropsychological and other data suggest a person may struggle with a particular endeavor, it can be a learning experience for the person to try it. If the person is resolved to make an attempt, professional resistance may lower rapport just when the person needs the most guidance. Professionals can help the person succeed to the degree possible. Still, the real world imposes consequences (e.g., being fired) with a stronger impact than the consequences that professionals can manipulate. The role of professionals in such circumstances is to be available for emotional support and to renew realistic planning. A non-judgmental approach is essential to accomplish this.

Professionals must modify counseling for the cognitive abilities of persons with brain injury (4). Professionals

have to consider the neuropsychological status of each person and adjust accordingly. There are numerous variables to weigh, including length of session (attention span), speed of speech (processing speed), sophistication of concepts or use of analogies (verbal reasoning), use of gestures (nonverbal processing), diagrams on a white board (visual-spatial ability), etc. One size does not fit all. Too often in health care for persons with brain injury, professionals pay insufficient attention to how well they are truly communicating; inadequate reflection on the actual impact of communication can destroy counseling effectiveness. Finally, it is important that there be consideration of professionals' characteristics and approach to counseling to insure a good match between professionals and persons with brain injury (55).

There are innumerable counseling approaches. It is impossible to discuss the application of all of them to brain injury. Still, many fall into one of three schools of thought: (85) cognitive-behavioral (e.g., Ellis' Rational Emotive Therapy and Beck's Cognitive Therapy), humanistic (e.g., Roger's Person Centered Therapy and Perl's Gestalt Therapy), and psychodynamic (e.g., Freud's Classical Psychoanalysis and Jung's Analytic Therapy). Very briefly, approaches from the cognitive-behavioral school focus on the facilitation of suitable, observable behavior and the alteration of thoughts that directly influence behavior; humanistic approaches emphasize self actualization, the growth of human potential, and the enhancement of the ability to experience one's feelings; professionals using psychodynamic approaches seek for people to increase control over unconsciousness influences and to understand the relationship between mental structures (85). Parenthetically, many rehabilitation professionals may be surprised at the inclusion of psychodynamic approaches. Yet, psychodynamically oriented therapists are increasingly addressing persons with brain injury (86). There are efforts to link research in brain function with psychoanalysis (87). Of course, psychoanalytical case conceptualization of emotional and behavioral functioning must recognize those issues that derive organically and not just attend to psychoanalytic formulation (88), but this is true of any psychological approach.

Professionals may choose to use approaches from any of these schools to assist persons with brain injury or they may decide to combine elements from more than one school. In the case of the more insight-oriented approaches (i.e., humanistic and psychodynamic) the premise is that insights garnered in treatment will change the perspectives of persons with brain injury. Such alterations should subsequently lead to emotional and behavioral improvement. This works best when persons with brain injury have sufficient cognitive processing ability to accomplish two aspects of this treatment. First, they should be able to formulate and express their thoughts and feelings. Second, they should be able to utilize changes in perspectives

to effect change in emotional responses and behavioral repertoire.

Threats to the former include aphasia, impaired vocabulary, verbal reasoning deficits, memory impairment, etc. Obstacles to the latter include deficits in divided attention, set shifting, memory, impulsivity, rigidity, etc. Sometimes, in fact, persons with brain injury can articulate, and believe, insightful perspectives, but organic impairment interferes with real world performance.

In contrast, cognitive-behavioral approaches seek to more directly correct actions and those thoughts that immediately attend upon behaviors. The principle is that efficacious behavioral improvement happens by a straight forward focus on requisite behavioral changes. This occurs most successfully when existential issues are less prominent, though professionals can use cognitive interventions to address existential issues. Furthermore, professionals vary in their emphasis on the cognitive versus behavioral end of the spectrum, either philosophically or on a case by case basis. In the more cognitive range, persons with brain injury often need abilities similar to those necessary to participate in insight oriented therapy. At the more behavioral tail, deficits in memory and learning can be impediments. In addition, recognition of the need to change is important, particularly for sophisticated behaviors that require complex social skills.

Skill building can be a corollary of counseling. This can entail skills that persons with brain injury develop implicitly from new insights gained in counseling or skills taught to them explicitly in counseling. Skill sets may range from cognitive compensation techniques to anger management skills to social skills (the latter will be discussed later in this chapter). In regard to cognitive rehabilitation, it behooves professionals to avoid artificial barriers between counseling and training in cognitive compensation methods. An integrated approach, using counseling combined with cognitive rehabilitation, should be part of professionals' armamentarium (89). For anger management skills, professionals should adapt the skills for the abilities of persons with brain injury (90).

## REHABILITATION PROCESS CHALLENGES

### The Importance of Early Attention to Psychological Variables

Rehabilitation is a formative time for persons with brain injury. Professionals can set the tone for the future experience of living with brain injury (91). Often, later in life, persons with brain injury still reflect on their early experiences (92–94). Sometimes there is gratitude; sometimes there is anger; sometimes there is disappointment.

Early assessment and intervention for emotional and behavioral concerns can help influence the direction of care and the perspectives of persons with brain injury.

In some settings, consultation on emotional or behavioral variables occurs only after there is a problem. In such places, prophylactic evaluation and case involvement by professionals with expertise on these issues is deemed secondary to initiation of physical, occupational, speech, and recreational therapies. This is unfortunate.

The gold standard for rehabilitation ought to be the automatic inclusion of evaluation and treatment of emotional and behavioral variables. Treatment teams should act proactively and avoid waiting for these problems to develop (46, 47). It is an error to assume that rehabilitation and accompanying adjustment on the part of persons with brain injury will proceed smoothly. Rather, professionals should function with the premise that brain injury is likely to be devastating, entailing cognitive, behavioral, and emotional traps, until the course of a case proves otherwise.

There are numerous benefits that accrue from this perspective. To begin with, professionals can detect behavioral and emotional issues as they start to initiate early intervention. For example, professionals can address depression before it becomes overwhelming or noncompliance before it is entrenched. It is easier to gently help re-conceptualize concerns as they emerge than to have to terraform the emotional and behavioral landscape.

Furthermore, guidance in how persons with brain injury conceive rehabilitation and their interactions with professionals can enhance the impact of other therapies. Professionals can facilitate motivation and effort in treatment. Willingness to perform necessary skills may otherwise be given less attention in rehabilitation than is acquisition of those skills. Knowing *how* to do something does not automatically imply *wanting* to do something, even if it is beneficial and necessary.

Finally, it is advantageous to include emotional and behavioral assessment and intervention at the start of rehabilitation so that persons with brain injury view attention to those variables as a natural part of everyone's rehabilitation. This removes the stigma of being singled out for help with emotional and behavioral responses to rehabilitation and brain injury. It also allows time to build rapport before any difficulty starts so that a relationship is in place on which to build further treatment, if necessary. In essence, evaluation and treatment of behavioral and emotional issues ought to be a standard, automatic component of rehabilitation, initiated upon admission to rehabilitation.

### Goal Setting

Rehabilitation is a collaborative effort requiring input from professionals, families, and persons with brain injury, among others. In intensive care units, the relationship of professionals to persons with brain injury is one of parent to infant, with professionals keeping the person alive.

In acute care settings, the relationship is one of parent to child, with professionals providing care and nurturance. However, in rehabilitation the relationship ought to be adult to adult, with professionals bringing knowledge and experience to a shared endeavor that includes recognition of the contribution of persons with brain injury. Fortunately, there is an increasing awareness of the importance of viewing treatment as a joint venture. For example, in the realm of behavioral treatment, the model of utilizing positive supports (74) to achieve successful behavioral functioning is based on an alliance with the person with brain injury. It takes a conceptual shift to view persons with brain injury as partners (95). Professionals' attitude toward persons with brain injury can have a large impact on treatment (46). In addition, it is essential that professionals be cognizant of cultural variables (96).

Professionals have a responsibility to avoid interpreting system problems, including societal attitudes or funding challenges, as organically imposed limits, while still facilitating awareness of organically determined limits. On one hand, it is unfair for professionals to be overly restrictive because of system issues or biases while, on the other hand, it is a failure of treatment to ignore anosognosia or unawareness, allowing pursuit of goals that really are unobtainable. Accurate feedback is good care, but being accurate (not over- or under- inclusive of limits) and compassionate (not too harsh in one's presentation) can be a challenge for professionals.

### Family Issues

Families are ordinarily unprepared to cope with brain injury. In part, there is a mismatch between their expectations for treatment outcome and the reality of recovery after brain injury. In our society, families expect the health care system to cure people after injury or at least leave them with minimal residual problems. Mass media, such as television, promulgate this expectation. Television portrays miraculous recoveries after all sorts of injuries, including brain injury. Rarely do shows demonstrate the true aftermath of brain injury. In addition, families' own experience with health care after acute illnesses fosters this expectation. When families take a child with an earache to their physician, they anticipate that the physician will cure the child, not that the child will be permanently deaf. When people break bones, they expect their physician to fix them, and they anticipate they will have little residual difficulty. However, when families experience the onset of a chronic condition in a loved one (e.g., spinal cord injury, kidney failure requiring recurrent dialysis, diabetes, AIDS, brain injury), there is no eventual cure and families do not know what to do. Persons with brain injury are not cured even when families, employees, friends, insurers, physicians, professionals, etc. all fulfill their roles and provide excellent help.

Families are unequipped for a health condition that violates all of their expectations and that requires them to adopt roles for which they had no previous training. They can feel resentment at the failure of the societal compact regarding health care. They perform their *acute* care roles (visits to the hospital, time off work, support of compliance with the treatment and medications, etc.), and yet the health care system fails them (i.e., there is no cure). Dr. Sanders' chapter on family intervention addresses family issues more thoroughly, but the impact of families' functioning is pertinent here in so far as it affects the psychological and behavioral status of persons with brain injury.

It is incumbent upon professionals to provide assistance to families if they wish to achieve successful rehabilitation. They should address the families' anger and frustration with the health care system. In addition, families may need help with their own guilt over their failure to protect their loved one from harm before onset and their powerlessness to obtain a cure afterwards (97). Professionals can help by exploring reasonable expectations for families and encouraging appropriate roles.

For example, many families attempt to be ever-present during rehabilitation, similar to their behavior during acute illnesses. This is detrimental to families because they are unable to maintain such vigilance indefinitely, despite feeling that they should be able to do so, and they burn out. Professionals can assist families to accept that involvement at a reduced level that can be maintained for years is better than total involvement early, with burn out shortly past acute rehabilitation.

Families may ignore their own needs (98). Yet, all aspects of caregivers' lives may be altered after brain injury (9). Moreover, there can be stressful changes not just for the primary caregiver, but for other relatives as well (99). While some family members may do relatively well, (100) the greatest stressors relate to behavioral, personality, and emotional changes in their loved ones after brain injury (101). Families may go through a crisis in how they relate and interact (102).

Professionals should also be alert for another scenario. Sometimes families have unresolved issues regarding the nature of behavioral care of their loved one, either during hospitalization or in the years following rehabilitation. When family members struggle with the necessity of implementing behavior plans, their needs merit attention. Their untoward reactions to behavior plans can range from disagreement accompanied by withdrawal to efforts that directly undermine behavior plans. This problem is similar to the challenge that professionals encounter with family agendas, sometimes hidden, that are at odds with professionals' other treatment efforts. For example, families may render assistance with return to work ineffective because of their own emotional needs (55) or there may be enabling issues interfering with chemical

dependency treatment. Of course, usually family members are strong allies in the implementation of behavioral treatment, and they are frequently quite insightful about how to proceed, but occasionally families need help to engage appropriately.

Despite the overwhelming nature of brain injury for families, professionals can greatly impact family perspectives after injury onset. For instance, a structured program that focuses on helping families can positively address the need families have for health information and emotional, community, and professional support (103). Obviously, families' need for help continues after acute rehabilitation. Families can benefit from ongoing support and guidance, even when professionals provide it by phone (104). Still, it can be very difficult to relieve family stress when behavioral dyscontrol persists (105).

## SELECTED APPLICATIONS

For a variety of issues in rehabilitation, emotional, behavioral, and neuropsychological assessment underlie the application of contingency, environmental, and counseling techniques, in conjunction with family intervention. The need to assess and treat some issues seems to arise repeatedly. A comprehensive review of all psychological difficulties is unfeasible here, but selected topics are worthy of mention.

### Aggression

Physical aggression may be the most distressing of all brain injury symptoms to other people. People will tolerate memory problems, depression, or the need for a wheelchair, but they will not permit physical assaults. When physical aggression occurs it commands attention.

As the severity of aggression increases, it requires an increasingly comprehensive approach. Environmental change can address the antecedents of aggression. The main variable to manipulate in a stimulus control paradigm is the behavior of professionals and other people. As already noted, their behavior often proves to be the primary antecedent for physical aggression.

Contingency techniques can be used after physical aggression, though they may prove more useful as an adjunct to antecedent control. Recall, however, the challenges in applying contingency procedures after brain injury. Moreover, when persons with brain injury direct aggression at professionals, it is particularly tempting for some professionals to be punitive. In this sense, contingency techniques can be notably difficult for professionals to positively and correctly implement.

Counseling with persons with brain injury can be essential to facilitate interpretation of antecedent and

contingency changes, the utilization of skill based techniques for anger management, cognitive restructuring of frustrating events, and preparation for future stressful events. Counseling can decrease errors and enhance error-less learning.

It is essential that professionals attend to variables that influence the expression of aggression. Treatment is less likely to be successful if two different people who apparently exhibit the same behavior receive the same treatment without an understanding of the behavioral etiology. Professionals must attend to the contribution of emotional variables leading to aggression and not just focus on the superficial behavioral symptom of aggression. Similarly, cognitive processing often plays a crucial role in the expression of aggression.

Families need particularly attentive support when there is physical aggression. Aggression may embarrass or frighten family members, especially when it is directed at the family. Professionals may need to encourage family members to consider their own safety. Alternatively, professionals may need to work with them regarding their own stimulus value and behavior as an environmental antecedent.

### **Noncompliance**

Noncompliance is a difficult problem for professionals. The obstacle to avoid is the automatic assumption that noncompliance is an intentional challenge to authority. Noncompliance can be due to a variety of factors. These include true dyscontrol (in which refusal is based on post-onset organic difficulty with acquiescence), manipulation for secondary gain, communication or memory deficits, pre-morbid oppositional personality, or attempts to reassert self-determination. It is also easy to miss the contribution to noncompliance of fatigue and poor sleep, depression, and initiation or impulsivity problems. As with all behaviors, determination of behavioral etiology is paramount for intervention.

Intervention may be multifaceted. Avoidance of power struggles is important. Education about the implications of noncompliance can be useful, particularly when unawareness is present. Sometimes negotiation can determine alternatives to achieve creative solutions. Alterations in schedules or the use of reminders, as well as other environmental changes can be successful.

Unfortunately, noncompliance can lead to paradoxical outcomes for persons with brain injury. Other people may view noncompliance as evidence for the need to restrict independence, despite its occurrence as an effort by persons with brain injury to expand their choices. They want the freedom to choose, and other people want to control poor choices. Treatment of noncompliance requires a careful balance of necessary rules and maximization of personal choice.

### **Impulsivity**

Impulsivity can be a particularly frustrating behavior for professionals and families, and, for that matter, for persons with brain injury. For professionals and families, impulsivity is difficult to address because it crosses other behaviors (e.g., social inappropriateness, risk to elope, suicidal ideation, noncompliance, hoarding, physical and verbal aggression) causing a worsening of whatever symptoms would occur anyway. For persons with brain injury, impulsivity can be embarrassing if there is sufficient self-awareness, because they act contrary to how they might otherwise behave. Oftentimes, upon post hoc guided reflection, persons with brain injury will express regret regarding impulsive behavior.

Two scenarios exist regarding impulsivity. First, persons with brain injury may act too intensely or prematurely. The resulting behavior appears as "too much, too soon." The behavior is too much of a good thing. Professionals find themselves trying to modulate behavior that would be acceptable if performed in a different setting, more slowly, or less intensely. Second, persons with brain injury may fail to stop inappropriate behavior, acts that ought not to occur at all. Professionals tend to describe these behaviors as risky or dangerous to persons with brain injury or to other people. There is a failure to inhibit impulses toward aggression, elopement, suicide, etc. Behavior in the first scenario appears as overly activated responses, and behavior in the second situation presents as uncontrolled behavior. Persons with brain injury find themselves being told to slow down in the first instance and stop in the second case. Impulsivity, therefore, may represent over activation or under control (48).

Impulsivity would appear to be a prominent component of the complaint of personality change after brain injury (106). It is likely to contribute to some of the more troublesome behaviors of aggression, sexual acting out, verbal abuse, etc. Moreover, the negative consequences associated with such behaviors tend not to alter their occurrence when impulsivity is a factor (74). As such, environmental changes, decreasing stimuli associated with impulsive responding, and skill building, when appropriate, may be more effective.

### **Depression, Grief, Catastrophic Reaction, and Post-Traumatic Stress Disorder**

Many persons with brain injury experience depression, (107) and the risk of suicide increases after brain injury (108). Depression can worsen as time passes post onset (109) and may correlate with increases in awareness or setbacks in the real world. Depression may be related to loss of self-esteem, uncertainty about the future, disruption of social supports, or particular events (e.g., loss of job). There are neuroanatomical and neurochemical factors as well, (11) and it is unclear as to whether depression after

brain injury is the same phenomena as depression without brain injury (107). Moreover, grief ought to be considered separate from depression *per se* (23). In light of experimental findings of brain activation during grief, (110) persons with brain injury may experience or demonstrate grief differently than others.

Furthermore, the typical stages of grief seen when people contemplate death may not apply well to the experience of brain injury (111). Rather, the emotional responses to brain injury may be better conceived as an identity crisis (112). However, the crisis may persist as the injury requires continual adaptation. There is an ongoing dynamic between brain injury and changing life circumstances, and it requires recurrent adjustment. This is characterized by uncertainty and has been described as a “mobile-mourning” process (113). Even after acute recovery, brain injuries do not appear static for many persons with brain injury. As they counter new life situations, unsuspected aspects of their injuries emerge to challenge them.

In addition, the people in the support system available to persons with brain injury are usually unprepared for survival of the person with alterations in cognitive, emotional, and behavioral functioning. They are unprepared to help. There is no known societal role for them to follow (114). As with persons with brain injury, family grief does not follow an orderly progression to resolution (97).

Persons with brain injury may also experience a catastrophic condition (115). They face lack of self actualization. This arises when impairment in abstract conceptual ability interferes with their accounting for performance failure on various tasks or activities. The resulting discord between impaired ability and an acceptable self-formulation of their shortcomings leads to the catastrophic condition and anxiety.

Deft handling of the catastrophic condition, or reaction, is important for successful rehabilitation. Pushing activities that highlight deficits and enhances struggles, or failures, can be contraindicated. In fact, two of the foundations of “Holistic Habit Retraining,” (69) a neurorehabilitation methodology, are errorless learning and a supportive approach, to help avoid the anxiety, frustration, despair, and resignation of the catastrophic condition that would otherwise interfere with learning.

Professionals must remain cognizant of the potential of catastrophic reactions as person with brain injury become more aware of deficits. There is the potential for catastrophic reactions as they advance from impaired self awareness to some awareness or to denial of deficit (116). Professionals may encounter accusations that they are making persons with brain injury worse during rehabilitation as awareness increases. This may be accompanied by a range of responses including withdrawal, noncompliance, resistance, anger, hostility, and aggression as persons with brain injury struggle with a mixture of perplexity and increasing despair.

Catastrophic reactions may vary in their presentation (117). In one scenario persons with brain injury may feel overwhelmed while experiencing shame, anxiety, and hopelessness. The loss of sense of self can drive frustration. Alternatively, in a second situation professionals may primarily observe passivity and withdrawal. Affect can appear flat. In a third variation persons with brain injury may respond with aggression and acting out behaviors (e.g., chemical abuse). There is likely to be hostility and resentment. In a fourth presentation there may be efforts to mask anxieties through superficial acquiescence and attempts to hide difficulties. This may prove difficult to maintain, however, since it requires persistent concealment of problems. In all instances persons with brain injury are attempting to cope with the underlying loss of integrity of the self. Finally, it should be apparent that any given person may have a combined clinical picture.

The development of post traumatic stress disorder (PTSD) is an additional factor that can complicate the care of persons with brain injury (118). There is documentation of PTSD after brain injury; (119) yet, there is debate regarding the co-occurrence of PTSD and brain injury (120) since traumatic brain injury can result in loss of consciousness and amnesia. Researchers have proposed avenues for the evolution of PTSD, however (121, 122). PTSD could arise from implicit memories occurring without conscious recall. Conditioned fear could cause PTSD in some cases. There may be later cognitive representations that lead to PTSD symptoms. Also, stressful events subsequent to immediate onset may be the basis for PTSD. Finally, neurobiological changes may contribute to PTSD.

### Social Skills

Social skills are a broad set of human interaction variables. They range from relatively narrow elements, such as eye contact or gestures, to broader factors including sensitivity to context and language-communication skills. Professionals need to address social self regulation (e.g., disinhibition, inertia), social self awareness (i.e., knowledge of one’s impact on other people), social insensitivity (i.e., understanding another person’s perspective or emotions) and social problem solving (i.e., interpersonal issue resolution) (123). Without social skill competency, brief, seemingly simple, everyday exchanges become episodes of miscommunication and sources of frustration. Worse, the lack of proficiency in social skills impairs the establishment or maintenance of ongoing supportive relationships.

It is important to recognize that social skill enhancement is challenging for a number of reasons. First, underlying cognitive deficits can impair learning new skills or remembering to apply them. Second, emotional factors, such as anger or frustration, or social pressure, such as

the desire to perform in a certain fashion to impress someone else, can distort how persons with brain injury perform skills. Third, persons with brain injury may relapse back to older, more over learned, dysfunctional skills.

Fortunately, research shows that persons with brain injury can learn skills for the social setting (124). This may involve specific skills, though there may be an increased difficulty in acquiring complex skills (125). When behavioral dyscontrol has resulted in the attainment of desirable goals in the past, then training in socially acceptable alternative methods to reach the same goal can mitigate behavioral problems (68). In the broader context of the utilization of social ability, social participation is also a function of perceived self-efficacy and determination, as well as energy level (126). Training can focus on general social competency that involves learning underlying principles for communication and social skills (127).

### Substance Abuse

Psychological considerations play a role in the treatment of substance abuse following brain injury. Professionals are likely to encounter three common patterns: social users whose use remains unchanged, but whose brain can no longer tolerate even a social level of consumption; social users whose use increases after onset, becoming abusive; and pre-onset abusers whose use remains abusive (and whose use may have contributed to their injury onset). Regardless of the amount and pattern of use, the best advice is abstinence: "zero, forever."

Still, it can be a considerable challenge for professionals to help persons with brain injury achieve abstinence. There are tremendously strong factors encouraging the use of alcohol and illicit drugs, including poor insight, denial, lack of information, peer pressure, depression, addiction, etc. Some persons with brain injury even report that the place they feel most normal is a bar, where their brain injury symptoms, including slurred speech, balance problems, memory difficulties, and social-sexual forwardness are commonplace among patrons without brain injuries. Hence, early discussion of chemical use and integration with other rehabilitation efforts helps set the stage for any future more comprehensive intervention.

Elsewhere in this book, Dr. Corrigan devotes a complete chapter to substance abuse. However, from a behavioral standpoint two concerns bear comment. The message of abstinence should be consistent across all professionals and family members. To be successful, professionals have to be attentive to issues of co-dependency (128). Moreover, professionals should be aware of any family members who may also have substance abuse problems and who will be unreliable participants in providing a united front on this issue.

Second, at times persons with brain injury may reject treatment advice. There are three typical objections: past adverse treatment experiences, claims of familiarity with chemical dependency treatment messages, or resistance to time away from community integration. Professionals must prepare to answer these concerns. Specialized programs for persons with brain injury who have substance abuse problems should differ from past treatment programs sufficiently enough so as to address the first two objections.

Persons with brain injury often experience frustration in traditional programs because of cognitive processing variables. They struggle in group treatment that fails to accommodate comprehension, language, memory, and processing speed variables. Furthermore, many persons with brain injury require help with abstinence because of their injury, not because of pre-morbid life devastation due to drugs or alcohol (e.g., alcohol use may have been at acceptable social levels prior to onset). It is important to remember that many persons with brain injury incur their injuries unrelated to any chemical use on their part (e.g., falls, sports, motor vehicle crash victims). Hence, traditional program messages regarding the need to redesign a dysfunctional life seem inappropriate to many persons with brain injury.

The integrated inclusion of a spiritual aspect in some programs can also be a difficulty. Some persons with brain injury, while accepting the need for treatment to achieve abstinence, reject faith-based messages in their brain injury recovery. This may be a function of their religious beliefs or the course of their emotional or psychological healing.

Finally, traditional follow-up support groups do not always readily welcome persons with brain injury and other participants may relate poorly to the experiences of persons with brain injury. Persons with brain injury may find that their social skill difficulties are at times misunderstood. Their cognitive problems can frustrate other group members.

Therefore, specialized programs can help after brain injury by structuring care around the cognitive needs of persons with brain injury and by tailoring their message to fit the circumstances of persons with brain injury. Also, professionals should have available materials that cover chemical use and brain injury. For example, it can be helpful to use workbooks specifically designed for chemical use after brain injury (129–131) or, if using a 12-step program, to use the 12-steps modified for persons with brain injury (132).

Professionals will find it easier to respond to the third objection (time away from community reintegration) when they link chemical health treatment to rehabilitation for brain injury. If professionals present it as a component of the overall plan of brain injury recovery, persons with brain injury may view it as more acceptable.

## SUMMARY

Issues of emotional and behavioral functioning require significant attention on the part of professionals. These concerns can influence the outcome of rehabilitation and can have a significant impact on persons with brain injuries and their families. Yet, there are forces ranging from insurers' perspectives to the inherent complexities in addressing psychological variables that impede treatment. Professionals will most benefit the people they serve when they are diligent about providing care for psychological needs.

Professionals should base intervention on solid assessment. This ought to include clinical observation, interview, and psychometric assessment of cognitive, behavioral, and emotional functioning. There is an array of possible intervention strategies. Treatment techniques include contingencies, environmental manipulation, counseling and skill building. Professionals should be aware of the advantages of starting care early after onset, the needs of families, and the nature of goal setting after brain injury. In fact, throughout behavioral care, during every type of evaluation and treatment for all emotional and behavioral problems, professionals must keep in the forefront of their decision making the unique nature of brain injury and its interaction with psychological functioning.

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# 45

## Neuropsychiatric Aspects of TBI

*Thomas W. McAllister*

### INTRODUCTION

To the casual observer deficits in speech and language function or ambulation may be the most readily apparent changes after a traumatic brain injury (TBI). However it is often changes in personality and behavior that cause the most distress to survivors and their family/caregivers. Such alterations in the core sense of who the individual is, or who their loved ones believe them to be, can be devastating. Frequently these issues are the rate-limiting step in various rehabilitation settings, interfere with return to work and the ability to achieve the maximum quality of life within the least restrictive environment (1–6). The cost to the nation in care expenditures, lost productivity and family disruption is staggering (7).

Some individuals with mild traumatic brain injury and virtually all individuals who survive moderate and severe TBI are left with significant long-term neurobehavioral sequelae (8–10). The reduction in TBI-associated mortality rates over the last several decades (11) has led to a significant increase in the number of individuals with long-term neurobehavioral disorders related to TBI (5, 12). In addition to the agitation, aggression, and confusion often seen in the acute recovery period, TBI is associated with an increase in the relative risk of developing many psychiatric disorders including mood disorders, psychotic disorders, anxiety disorders, obsessive-compulsive disorder

and others (13–16). TBI may well be a critical risk factor in the development of schizophrenia in those with a genetic vulnerability to this illness (17).

Even apart from formal psychiatric disorders, behavioral challenges abound. Syndromes such as apathy, disorders of impulse control and affect, though perhaps not meeting formal criteria for specific psychiatric disorders are a source of excess disability. Environmental and psychosocial factors play key roles in the genesis and maintenance of these neurobehavioral problems, but so does the profile of regional brain injury.

The overarching theme of this chapter is that the assessment and treatment of the neurobehavioral sequelae of TBI follow logically from an understanding of the typical profile of traumatic injury. Thus the relationship of the neuropathophysiology of TBI to the neurobehavioral sequelae commonly encountered by individuals with TBI is outlined. An approach to the evaluation and treatment of these sequelae is suggested.

### RELATIONSHIP OF PROFILE OF INJURY TO NEUROBEHAVIORAL SEQUELAE

Our knowledge of the neuropathophysiology of TBI has increased dramatically over the last decade (18). Advances in molecular biology, molecular genetics, neuroimaging,

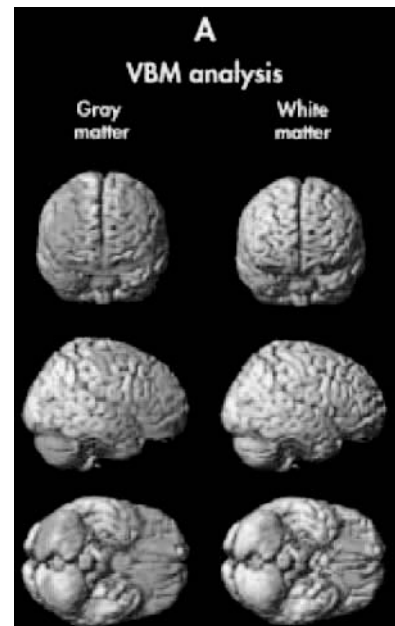
neuropsychology, and other neurodiagnostic techniques make possible a much finer resolution of brain injury profile associated with specific neuropsychiatric sequelae. The neuropathophysiology of TBI is more thoroughly discussed in chapters 6–8 (18). It is important to highlight some features of the neuropathology of TBI in that they help to explain the special vulnerability to neurobehavioral challenges seen in TBI survivors.

In brief, most injuries result from the brain coming into contact with an object (which might include the skull, or some external object) or from rapid acceleration or deceleration of the brain. Contact mechanisms often result in damage to scalp, skull, and brain surface (e.g., contusions, lacerations, intracerebral hematomas) (18). Acceleration/deceleration mechanisms are associated with shear, tensile, and compression forces that have maximum impact on axons and blood vessels resulting in axonal injury, tissue tears, and intracerebral hematomas. Injury from both mechanisms occurs immediately (referred to as primary injury) and may also evolve over time due to a variety of factors including massive release of neurotransmitters with subsequent triggering of excitotoxic injury cascades, and other injury-related factors such as hypoxia, edema, and elevated intracranial pressure (referred to as secondary injury).

With respect to brain tissue, contact mechanisms tend to produce focal injuries such as surface contusions and lacerations. In addition, rapid acceleration or deceleration results in differential motion of the partially tethered brain within the skull. Surface contusions can thus be seen where the swirling motion of the brain comes into contact with bony protuberances on the interior of the skull. Frequent sites of such injury are the anterior temporal poles, the lateral and inferior temporal cortices, the frontal poles, and the orbital frontal cortices. Acceleration and deceleration mechanisms also produce more widespread or diffuse injury (“diffuse axonal injury”) to white matter. Particular areas of vulnerability include the corpus callosum, the rostral brainstem, and sub-frontal white matter (18).

Secondary injury appears to occur at least in part from mechanical distortion of the neurons resulting in massive release of neurotransmitters. Although this probably occurs throughout the brain, the excitotoxic cascades and other forms of secondary injury such as hypoxia/ischemia have a disproportionate effect on certain brain regions such as the hippocampus, even in the context of an otherwise fairly mild injury (19).

Thus the typical profile of injury involves a combination of primary injury (occurs at time of application of force) and secondary injury (evolves over time subsequent to the primary injury) as well as a combination of focal and diffuse injury. Furthermore, although the damage may be diffuse or multi-focal, there are certain



**FIGURE 45-1**

Results of voxel-based morphometry demonstrating areas of reduced gray and white matter density in individuals with TBI compared to controls. Red areas show frontal and temporal abnormalities. From Bigler E. “Structural Imaging.” In Silver JM, McAllister TW, Yudofsky SC (eds). *Textbook of Traumatic Brain Injury*. American Psychiatric Press, Washington D.C. 2005, p. 87. Used with permission

brain regions which are highly vulnerable to injury and account for the high rate of challenging behaviors and the increased rates of psychiatric illness that are associated with TBI. These include the frontal cortex and sub-frontal white matter, the deeper midline structures including the basal ganglia, the rostral brainstem, and the temporal lobes including the hippocampi (see figure 45-1).

### RELATIONSHIP OF TBI INDUCED NEUROTRANSMITTER CHANGE TO NEUROBEHAVIORAL SEQUELAE

In addition to the profile of regional brain injury described above there is evidence that neurotransmitters with important roles in modulating common neurobehavioral sequelae of TBI (such as regulation of mood, anxiety, motivation, impulse control, and aggression) are altered in TBI. This evidence is briefly summarized to set the stage for rational psychopharmacological interventions for these sequelae.

**Catecholaminergic System Changes** There is significant evidence for dysfunction of catecholaminergic systems associated with TBI (20–22). This is important because the catecholamines (epinephrine, norepinephrine, dopamine)

play critical roles in a variety of domains important in behavioral homeostasis. Animal studies and observations from the use of catecholamine agonists in clinical practice suggest that epinephrine and norepinephrine play important roles in arousal, cognition, reward behavior, and mood regulation (23–25). Deficits in central adrenergic tone and thus associated with deficits in arousal, attention, memory, motivated behavior (apathy), and mood regulation. Dopaminergic tone and proper dopamine signaling are particularly important in the modulation of motivated behavior, attention, and working memory (see (22, 26, 27) for reviews).

As noted there is evidence of disruption of catecholaminergic homeostasis after injury. TBI results in activation of the sympathoadrenomedullary axis with subsequent alterations in hemodynamic parameters and cardiopulmonary function. Plasma norepinephrine (NE) levels are elevated after TBI and this elevation correlates with injury severity indicators (28). Circulating levels of dopamine, norepinephrine, and epinephrine may be markers of injury severity and likelihood of recovery (20, 21). Animal models of TBI have also shown a relationship between injury severity, increasing circulating levels of epinephrine and norepinephrine, and secondary complications such as cardiac arrhythmias (29). Transient hypoxia, common in more severe injuries, can result in dramatic releases of hippocampal norepinephrine (30).

Animal studies suggest that alterations in dopamine, norepinephrine, and epinephrine levels can be prolonged after TBI, associated with alterations in catecholaminergic receptors in damaged cortical areas, and can impair catecholaminergic function after trauma (29, 31). Administration of certain catecholaminergic agents may enhance recovery from brain injury (32–34), even after one-time doses (32, 35–37). Conversely, catecholaminergic *antagonists* can slow rate of recovery from certain types of brain injury (38). Some agents that augment catecholaminergic tone reduce the cognitive effects of TBI in animal models. For example Zhu et al. (39) administered L-deprenyl, a selective and irreversible MAO-B inhibitor to rats subjected to combined fluid percussion TBI and entorhinal cortical lesions and found significantly reduced cognitive impairment (Morris water maze performance) compared to the rats treated with vehicle only. There is good evidence that in individuals with TBI, methylphenidate, which augments both the dopaminergic and adrenergic systems, is effective in ameliorating certain cognitive deficits (40). Another study (41) showed significant improvement in executive function tasks with bromocriptine, a dopamine agonist.

*Cholinergic System Changes* Central cholinergic tone is critical to the modulation of most cognitive and behavioral domains, appearing to facilitate signal to noise ratios. It is of particular importance however with respect to attention and memory (Perry and Perry 2004).

Alterations in central cholinergic tone may also play a role in the genesis of mood disorders, particularly depression (see (42)). Cerebral cholinergic neurons and their ascending projections are vulnerable to trauma (43). Acutely, cholinergic neurons release large amounts of acetylcholine. Subsequently there is evidence for long-term reductions in cerebral acetylcholine levels (44). Sudden release of acetylcholine at the time of injury may contribute to the extent of injury through facilitation of excitotoxic cascades. Cholinergic antagonists can be neuroprotective in models of TBI (see (43) for review). Several studies have shown damage to the nucleus basalis of Meynert, as well as reduced levels of choline acetyl transferase (a marker of cholinergic afferents) in brain regions vulnerable to trauma including temporal cortex, cingulate and posterior parietal regions in humans who died within several weeks of injury (43, 45–47). Post-synaptic muscarinic and nicotinic receptors remained intact (45–47), suggesting cholinergic agonists as a potential point of intervention for cognitive deficits (43).

*Serotonergic System Changes* Central serotonergic tone is important in the modulation of normal mood states and aggression. Medications that increase serotonergic function are effective antidepressants and anxiolytics, and can reduce the frequency and intensity of aggressive behavior. As with the catecholaminergic and cholinergic systems, the serotonergic system is activated in TBI with increased levels of serotonin evident in areas of significant tissue damage, and in association with lowered regional cerebral glucose utilization (18, 48–50).

*Summary* Several cortical regions including frontal cortex, temporal cortex, and hippocampus are particularly vulnerable to TBI. Furthermore sub-cortical white matter, particularly in frontal regions and the corpus callosum, are often damaged. In addition catecholaminergic, cholinergic, and serotonergic systems are vulnerable to disruption acutely and chronically in TBI. This profile of structural and neurochemical injury plays a direct role in the common neurobehavioral sequelae associated with TBI.

## CHANGES IN PERSONALITY

Survivors and family/caregivers frequently describe the effects of the injury as “changes in personality”. Lifelong patterns of responding to external cues, situations in the environment, and internal drives or motivations, can be significantly altered. This takes two different forms: exaggeration of pre-injury traits, or fundamental changes in response patterns. Within the latter category, careful inspection usually reveals that this can be further parsed into alterations in the frequency or intensity of predictable responses to environmental cues or stimuli, or unpredictable response patterns. Several common clusters of symptoms that characterize the “personality changes” are recognizable.

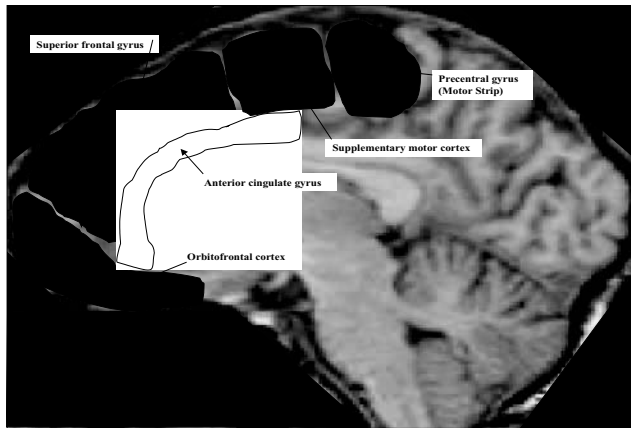


FIGURE 45-2

Mid-sagittal view of the brain showing prominent regions associated with executive functions. From McDonald et al. *Executive dysfunction following traumatic brain injury: Neural substrates and treatment strategies NeuroRehabilitation* 17 (2002) 333–344. Used with permission

**Dysexecutive Syndromes** Motivated behavior can be thought of as sets of behavioral responses that are more likely to occur than can be accounted for by chance alone. There are generally three components to motivated behaviors including initiation, procurement, and self-monitoring. These components, along with decision making, and mental flexibility are often referred to as executive functions. In fact much of the altered and distressing changes in behavior or personality after TBI can be subsumed under the rubric of impaired executive function (or “dysexecutive syndromes”) (see (51) for review).

Three broad (and somewhat overlapping) domains comprise executive functions:

- (i) *higher order cognitive function* (including mental flexibility, problem solving, set-shifting),
- (ii) *social comportment* (including context specific awareness of one’s behavior relative to past individual and societal norms, self-monitoring and self-correction), and
- (iii) *motivated/ reward-related behavior* (including initiation, sequencing, achieving/consuming).

As noted, these are not fully distinct domains but rather are more interactive and overlapping. This complex relationship is mirrored clinically in the observation that one can see individuals with prominent deficits in one, two, or all three domains to varying degrees. From the clinical standpoint, the prominent challenging behaviors brought to the clinician’s attention flow from these domains and can be usefully grouped into the following categories:

(i) Cognitive Syndromes

Cognitive deficits after TBI are covered in greater detail in Chapter 44. It is worth highlighting that initial and

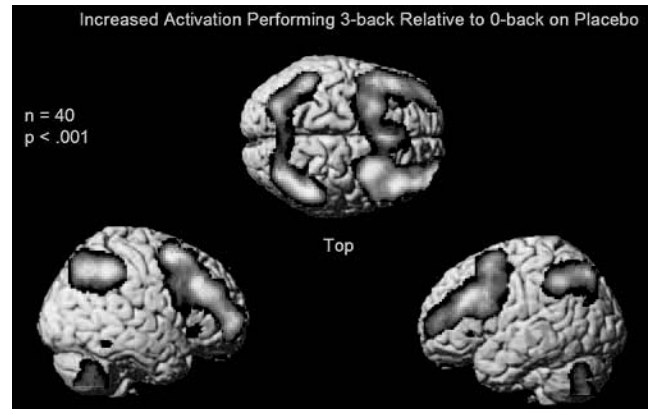


FIGURE 45-3

Activation of working memory regions as shown with functional MRI. The above image shows the mean group image of 40 participants performing a WM task (3-back). Note extensive yet selective bifrontal, biparietal, and cerebellar activation associated with the task

persistent cognitive deficits are the most common complaints after traumatic brain injury (TBI) (52, 53) and the major hindrance to normalization in the areas of independent living, social re-adaptation, family life, and vocational endeavors (54, 55). There are several predictable areas of impairment including short-term memory, speed of information processing, and attention (56–66). Obviously these are not completely independent domains, and in fact the typical profile of attention and memory deficits could be reasonably subsumed under the construct of working memory (WM), the ability to hold information in mind and manipulate that information in light of incoming information. Much progress has been made defining the circuitry and neurochemistry of WM (see McAllister et al. 2004 for review; (26, 67–69) and suggests that (1) the parietal cortices (70–73), (2) the frontal speech areas such as Broca’s area (inferior frontal gyrus) and the supplemental motor areas, and (3) the prefrontal area (74, 75) play major roles in WM function. The conceptualization of WM as a core deficit in TBI may have particular significance in that the brain regions implicated in WM circuitry are the same regions that are vulnerable to injury in the typical TBI.

(ii) Social Comportment

**Impulsivity** One of the more common concerns of patients and family/caregivers alike is that survivors have difficulty with impulse control. This can be manifested in verbal utterances, physical actions, snap decisions, and poor judgment flowing from the failure to fully consider the implications of a given action. This is closely related to the concept of stimulus boundedness in which the individual responds to the most salient cue in the environment or attaches exaggerated salience to a particular cue

without regard to previously determined foci of attention or priorities.

*Irritability* Another very common concern of patients and family/caregivers pertains to the modulation of anger. Survivors describe themselves as more irritable or more easily angered. Although a particular cue might be perceived as a legitimate aggravation of some sort, the response is characteristically out of proportion to the precipitating stimulus. Responses can range from verbal outbursts to dangerous aggressive and assaultive behavior. This modulatory deficit differs in intensity, onset, and duration from the pre-injury pattern for any given individual.

*Affective Instability* Survivors and family/caregivers frequently describe a change in affective stability characterized by exaggerated displays of emotional expression which seem out of proportion to both the precipitating stimulus and the injured individual's previous range of response to similar stimuli. Cues or events that previously might have elicited momentary sadness may now precipitate weeping or crying. Events which in the past might have provoked a frown or reply laced with irritation now result in loud angry verbal outbursts associated with marked sympathetic arousal. The hallmarks of this instability typically include a paroxysmal onset, brief duration, and an exaggerated intensity of response out of proportion to the precipitating stimulus. This phenomenon is common to a variety of disorders affecting the CNS and has been given a variety of terms including pathological affect, affective lability, pseudobulbar affect, and affective incontinence (see (76) for review).

*Awareness Deficits* The burden of the above changes in personality and behavior is often complicated by a surprising and at times devastating lack of awareness of these changes (see (77, 78) for reviews). The injured individual may be unable to appreciate that their behavior is different since the injury, in stark contrast to family/caregivers and providers who may be painfully aware that the injured individual has changed in fundamental ways and can often provide detailed lists of these changes.

Alternatively an individual with TBI may have a vague sense that he or she is different or "not who I used to be" and yet struggle to define the specific ways in which their behavior or personality differs from prior to the injury. Awareness is not a unitary concept (79) and thus it is important to characterize the nature and extent to which an individual suffers from this problem. Of particular interest to this discussion is that individuals with TBI are less likely to be aware of changes in behavior and executive function than changes in more concrete domains such as motor function (e.g., (80)). Furthermore the degree of awareness has been found to correlate with functional and vocational outcome in many (81–84) though not all studies (85).

As is the case with disorders of affective stability, problems with awareness of deficits are not unique to individuals with TBI but rather occur in a broad range of disorders of the CNS including severe and persistent mental disorders such as schizophrenia (78). The literature suggests that lack of awareness of illness is not simply a function of global cognitive deficits but perhaps is more related to frontal-executive dysfunction (86–88, 89–92). Studies of the neuroanatomical correlates of illness awareness deficits in these disorders, and in overlapping syndromes such as anosagnosia suggest that injury to certain brain regions carries a heightened vulnerability to awareness deficits (78). Stuss (93, 94) suggests that frontal systems generate self-awareness, self-reflectiveness, and self-monitoring. Other work has suggested that lack of awareness in schizophrenia is associated with selective structural brain changes, including smaller brain size and selective atrophy of certain subregions of the frontal lobes (77, 95). Furthermore, using a self-reflective task while undergoing functional MRI, Flashman et al. have been able to show very high correlations of degree of unawareness with frontal activation in individuals with schizophrenia (78). Because frontal systems also play a critical role in the modulation of key social skills and behaviors (e.g., initiation, motivation, problem solving, and affective modulation), frontal lobe damage can affect the ability to understand the impact that deficits have on day-to-day function and how to apply that knowledge to a current situation. In individuals with TBI, this dimension is frequently the focus of family/caregiver concern yet is often not recognized by individuals with TBI (5, 96–100). Even when the individual admits to some difficulties, he or she is often unable to predict the implications of these deficits in current or future social situations.

### (iii) Disorders of Motivation

*Apathy* The underlying deficit associated with apathy is in the realm of motivated behavior (101). Although not as overtly disturbing or alarming as some of the other changes in personality described above, it can be disturbing to family/caregivers, and is frequently the reason that injured individuals fail to progress in rehabilitation programs. Furthermore it is often misinterpreted as either laziness or depression and may be somewhat paradoxically linked to aggression when for example attempts to engage the individual in activities in which they have little interest can precipitate assaultive behavior (25).

Apathy is quite common after TBI. Kant et al. (102) found that apathy (mixed with depression) occurred in 60% of their sample of individuals with TBI. Andersson et al. (103) found that almost half of their sample of individuals with TBI had significant degrees of apathy. Deficits in motivated behavior can occur in association with injury to the circuitry of "reward" which includes behavior specific (thirst, sex, hunger) hypothalamic



centers (25, 104), and a more general reward system linking the forebrain to the midbrain. Key nodal points in this circuitry include the amygdala, hippocampus, caudate, entorhinal and cingulate cortices, the ventral tegmental area and the medial forebrain bundle. Catecholaminergic systems, particularly the mesolimbic dopaminergic system appear to play critical roles in the modulation of the reward system (see (25, 104) for reviews).

### RELATIONSHIP OF PROFILE OF INJURY TO PERSONALITY CHANGES

A full discussion of the neuroanatomical substrates of the above behaviors is beyond the scope of this chapter. However the link between the injury profile in a typical TBI and some of these behaviors is fairly simply understood.

Five major frontal-subcortical circuits have been identified, one orchestrating primarily motor function, one primarily oculomotor function, and three that have significant roles in non-motor forms of behavior (see (105, 106) for reviews). Each of the latter three circuits can affect motivated behavior, though in somewhat different ways. Each circuit is named for its site of origin in the frontal cortex (e.g. the dorsolateral frontal-subcortical circuit, the orbitofrontal-subcortical circuit, and the anterior cingulate-subcortical circuit) (see Figure 45-4). Each circuit follows a similar path starting from the site of origin in the frontal cortex projecting to the striatum, from there to the globus pallidus, then to the thalamus and back to the frontal cortex. Each circuit is thought to be a more or less closed loop with some additional input

from other functionally related brain regions. The circuits differ from each other with respect to exact pathways through the key nodal points. Thus for example the dorsolateral frontal circuit projects to the dorsal caudate, the orbitofrontal circuit to the ventral caudate, and the anterior cingulate to the medial striatum/nucleus accumbens respectively. Similar topographic differences can be traced through the globus pallidus and the thalamus as well.

Examination of the brain regions vulnerable to injury in the typical TBI and the neuroanatomical substrate of core cognitive and behavioral domains (executive functions, social comportment, motivation) suggests why these areas are so often a source of distress to survivors and their family/caregivers after TBI. The frontal-subcortical circuits responsible for these critical domains of higher intellectual function and empathic, motivated, nuanced human behavior are highly vulnerable to injury in the typical TBI. Damage to the dorsolateral prefrontal cortex and its circuitry impairs executive functions such as working memory, decision making, problem solving and mental flexibility.

Damage to the orbitofrontal cortex and related nodal points impairs intuitive, reflexive, social behaviors and the capacity to self-monitor and self-correct in real time within a social context.

Damage to anterior cingulate and related circuitry impairs motivated and reward-related behaviors. Injury to medial temporal regions further impairs other aspects of memory and the smooth integration of emotional memory with current experience and real-time assessment of stimulus salience. In short the profile of injury vulnerability predicts the neuropsychiatric sequelae of injury (see Figure 45-5).

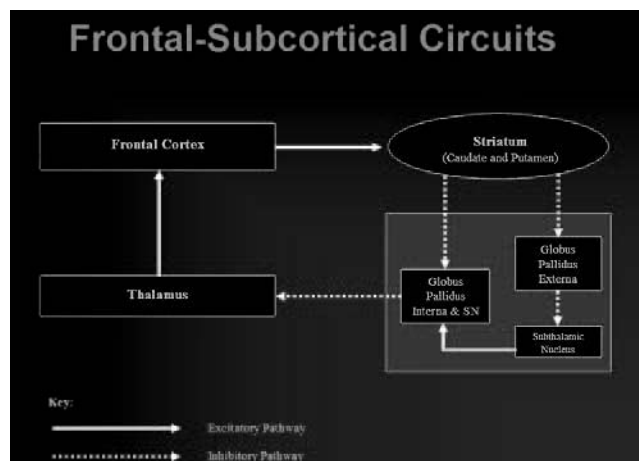


FIGURE 45-4

Outline of key nodal points in the five major frontal-subcortical circuits. Adapted from Arciniegas D, Beresford T. *Principles of Neuropsychiatry: An Introductory Approach*, Cambridge University, 2001. Cambridge, UK. p. 62. Used with permission

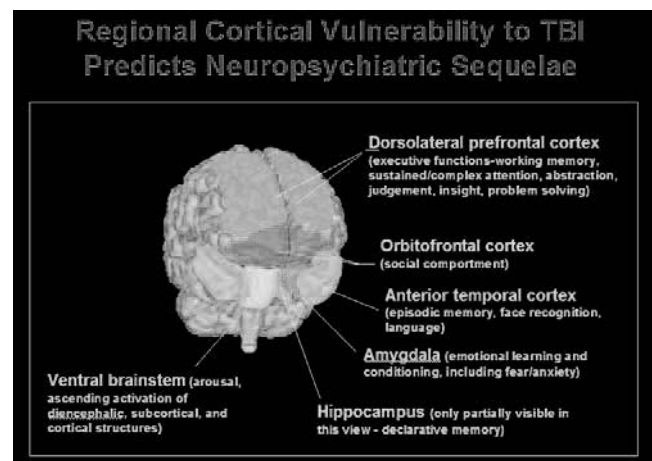


FIGURE 45-5

Relationship of brain regions vulnerable in typical TBI to predictable neurobehavioral sequelae. Adapted from Arciniegas D, Beresford T. *Principles of Neuropsychiatry: An Introductory Approach*, Cambridge University, 2001. Cambridge, UK. p. 370. Used with permission

This principle then should be the foundation on which a good neuropsychiatric evaluation is based. The process of elucidating the profile of injury, the profile of current signs and symptoms, and mapping the latter onto the former to assess goodness of fit is the work of the neuropsychiatric evaluation. Signs and symptoms which are not accounted for by the profile of injury must be explained on another basis or the profile of injury should be re-assessed. The clinical picture should make sense in the context of the brain damage.

### RELATIONSHIP OF TBI TO PSYCHIATRIC DISORDERS

In addition to the changes in cognition, behavior, and personality described above, a significant body of evidence suggests that TBI results in an increased relative risk of developing psychiatric disorders including mood and anxiety disorders, and psychotic syndromes (13, 15, 16, 107) (see Table 45-1). For example Koponen et al. (16) studied 60 individuals 30 years after their TBI and found that almost half (48%) developed a new Axis I psychiatric disorder after their injury. The most common diagnoses were depression, substance abuse, and anxiety disorders. Rates of lifetime and current depression (26%, 10%), panic disorder (8%, 6%), and psychotic disorders (8%, 8%), were significantly higher than base rates found in the Epidemiologic Catchment Area (ECA) study (108).

Hibbard et al. (15) studied 100 adults on average, 8 years after TBI. A significant number of individuals had Axis I disorders prior to injury. After TBI, the most frequent Axis I diagnoses were major depression and anxiety disorders (ie, PTSD, OCD, and panic disorder).

Almost half (44%) of individuals had two or more disorders. More recently (109) this group reported a longitudinal study of 188 individuals enrolled within four years of injury and assessed at yearly intervals on at least two occasions. Once again they found elevated rates of psychiatric disorders prior to injury. Subsequent to TBI, there were increased rates of depression, PTSD, and other anxiety disorders. This was particularly true of those with pre-injury psychiatric disorders. Furthermore, the rates were greatest at the initial assessment point after injury and stabilized or decreased over time (see Table 45-2). Van Reekum et al. (13) carefully reviewed the literature on the relationship of TBI to a variety of psychiatric disorders and using the ECA data for baseline rates concluded that TBI was associated with an increase in the relative risk for several psychiatric disorders (see Table 45-1).

Fann et al. (110) recently published findings on a cohort study of the medical records of about 1,000 HMO members who sustained a TBI classified as either mild (LOC <1hr) or moderate to severe, and followed for three years. Compared to non-injured controls, the individuals with TBI had increased indicators of psychiatric illness, especially in the first year after injury, and there was some evidence of a biologic gradient (49% in the moderate-severe group, 34% in the mild group, 18% in the non-injured comparison group). In injured individuals without history of psychiatric illness the Odds Ratio of developing psychiatric illness in the first 6 months was 4.0 in the moderate-severe group. Wei et al. (111) in a study of Medicaid beneficiaries in four states found that 18% of ~3,600 individuals diagnosed with TBI suffered severe mental illness, and another 16.5% had other mental disorders. Those with mental illness had significantly higher expenditures.

TABLE 45-1  
*TBI and Psychiatric Disorders*

DISORDER	TOTAL N (# STUDIES)	MAX DURATION OF FOLLOW-UP (YRS)	# WITH DISORDER	% WITH DISORDER	RELATIVE RISK
Depression	653(8)	7.5	289	44	7.5
Bipolar Affective Disorder	354(5)	7.5	15	4.2	5.3
Gen. Anxiety Dis	398(5)	7.5	36	9.1	2.3
OCD	282(3)	7.5	18	6.4	2.6
Panic Dis	282(3)	7.5	26	9.2	5.8
PTSD	441(6)	7.5	62	14.1	1.8

From van Reekum et al. Can traumatic brain injury cause psychiatric disorders? *J Neuropsychiatry* 12:316-327, 2000. Used with permission.

**TABLE 45-2**  
**Prevalence (%) of Axis I Disorders at All Time Points (109)**

DIAGNOSIS	COMMUNITY BASE RATES*	PRE-TBI (N=188)	T1 (N=188)	T2 (N=188)	T3 (N=188)
Depression†	6	20	35	24	21
Substance abuse‡	17	32	14	10	17
PTSD	8	10	30	18	21
Other anxiety§	2–13	16	27	19	9
Any other Axis I¶	–	5	9	5	0

From Ashman et al. Psychiatric challenges in the First 6 Years after Traumatic Brain Injury: Cross-Sequential Analyses of Axis I Disorders. *Arch Physical Medicine and Rehabilitation* 85:S36–42, 2004.

\*Bourdon et al.

†Includes major depression, depression not otherwise specified, and dysthymia.

‡Includes alcohol abuse, alcohol dependence, drug abuse, and drug dependence.

§Includes obsessive-compulsive disorders (OCD), panic, phobias, and generalized anxiety disorder (GAD).

¶Excludes depression disorders, substance abuse and dependency, PTSD, OCD, panic, phobias, and GAD.

### Diagnostic and Labeling Issues

It is important to address several issues with respect to the above studies and the question of psychiatric disorders in general after TBI.

*Symptoms vs. Disorder* As with any potentially disabling condition, individuals with TBI report a variety of symptoms in a variety of domains (discouragement, frustration, fatigue, anxiety etc). Not all of these symptoms will rise to the level of a disorder. However symptoms that are consistent and sustained over time (usually weeks), and that are of sufficient severity to interfere with social or occupational function or quality of life, are legitimately considered disorders. In the studies cited above, standardized criteria encompassing those principles were used and thus argue strongly that TBI acts as a gateway to the development of many psychiatric disorders. The consistent observation that individuals who sustain a TBI have higher base rates of psychopathology prior to injury suggests that there is a reciprocal interaction: psychopathology predisposes to TBI, and TBI in turn predisposes the individual to develop psychiatric disorders.

*Labeling Issues* Many individuals resist the idea that they have an illness. This is not unique to individuals with TBI, but rather reflects a general dislike of being labeled as having a disease. There is an even greater resistance to seeing oneself as having a psychiatric illness. Again this is equally true of injured and non-injured populations. However effective treatment can follow appropriate diagnosis. To avoid a diagnosis because of a societal or individual resistance to it is not in the interest of the individual suffering with the symptoms.

*Use of Diagnostic and Statistical Manual of Mental Disorders (DSM) Nomenclature* As with most diagnostic schemes the DSM approach has strengths and weaknesses. Its reliance on standardized phenomenological criteria has been helpful, particularly when sorting

out idiopathic psychiatric disorders. It is less helpful when approaching diagnosis in neuropsychiatric populations, including those with TBI. There are several reasons for this. In the DSM, psychiatric disorders in the context of neurological illness can be coded as “diagnosis” x “secondary to a general medical condition”. The use of the modifier “secondary to a general medical condition” implies that it is possible to accurately assess causality when for example a depressive syndrome follows a TBI by some time interval. Although this may be true, (and probably often is the case), proof is lacking and thus such a label reflects the impression or bias of the clinician.

The terms used to describe the changes in behavior and personality flowing out of damage to the various frontal-subcortical circuits described above are “personality change secondary to . . .”. Although this represents a significant improvement over “organic personality disorder” (DSM III), it does not do justice to the subtle and nuanced alterations present after a brain injury.

Perhaps most importantly the current schema does not recognize or allow for the alteration of syndromic presentations by brain injury. The question of how to diagnose depression in a non-verbal individual for example is not addressed in the DSM. The idea that depression can be expressed in other ways is not reflected directly in the menu of symptom options. For example so called “depressive equivalents” must be inferred by creative clinicians. Thus the diagnostic schema requires further refinement that hopefully will be reflected in future editions of the DSM. Despite these limitations it is helpful to review what is known about the association of TBI and certain psychiatric disorders.

### MOOD DISORDERS

*Depression* Depression after brain injury is common, with estimates that 25–60% of individuals with TBI

experience a depressive episode (DSM-IV criteria) within 8 years of injury (15, 112). These rates do not take into account individuals who have depressive symptoms but who fail to meet DSM-IV diagnostic criteria. It is also important to note that depression is associated with poorer cognitive, social, and functional outcome (112, 113) and can act as an amplifier of other neurobehavioral challenges including anxiety and aggression (7, 15, 112). The increased rate of depression and associated symptoms in TBI compared to other injuries suggests that CNS trauma and/or factors in plasticity/repair may play a role in the genesis of mood disorders.

*Neural Circuitry of Depression* Over the last decade substantial progress has been made in outlining the brain regions and related circuitry of mood regulation (see (114–116)), and not surprisingly they overlap with the areas vulnerable to the typical TBI. A thorough review of this topic is well beyond the scope of this chapter but several points are worth noting. Much of the insights come from functional imaging studies (see Refs. 114, 117 for thorough discussion) that have indicated metabolic abnormalities in dorsolateral prefrontal cortex (DLPFC) and anterior cingulate (reduced activity), and ventrolateral prefrontal cortex (increased activity) associated with depression. Although there is some variability of findings, other regions including temporal lobe and basal ganglia have also been found to have reduced activity (114).

A second group of studies has explored induced changes in mood state in depressed patients before and after manipulations such as sleep deprivation and tryptophan depletion, or before and after induced sadness in healthy individuals. The weight of evidence from these studies suggests that interventions leading to a less depressed state are associated with increased activity in DLPFC and anterior cingulate, and decreased activity in ventrolateral prefrontal cortex – largely consistent with the resting baseline studies (see (114)). Taken together this evidence suggests that the two frontal-striatal-thalamocortical circuits originating in orbitofrontal and dorsolateral prefrontal cortex function abnormally in depression. It may be that the orbitofrontal circuit with its limbic connections is the substrate of disordered emotional processing and vegetative symptoms common in depression, whereas dysfunction in the dorsolateral circuit may result in the cognitive deficits associated with depression (114, 116, 117).

*Neurochemistry of Depression* Several neurotransmitter systems play key roles in normal mood regulation and depression. Evidence of monoamine dysfunction in depression comes from the putative mechanisms of action of antidepressant compounds, most of which increase release, block re-uptake, or interfere with metabolism of norepinephrine, serotonin, or dopamine (see (118) for recent review). Interventions that reduce central monoaminergic tone (for example the

medication reserpine) are associated with an increased rate of depression. However, it is clear that a simple “imbalance of monoamines” explanation is inadequate. Several drugs (e.g., CNS stimulants) increase release of monoamines but are poor antidepressants. The effects of antidepressant compounds on monoamine transmitters can be demonstrated within hours, yet the mood altering effects take several weeks and not all depressed individuals respond equally to the same antidepressant. Thus, much remains to be learned.

An alternative theory of the genesis of depression posits that there is an imbalance of cholinergic and adrenergic tone with a relative cholinergic hyperactivity (see (42)). There are several reasons to postulate a role for cholinergic systems in mood regulation. Relative to healthy controls, depressed patients have a variety of exaggerated physiological responses to cholinergic agonists. The cholinergic agonists arecholine and physostigmine induce dysphoria in normals and can worsen depressive symptoms in individuals with mood disorders (42). The majority of antidepressants, including the tricyclics and SSRIs, have anticholinergic properties. Recent magnetic resonance spectroscopy (MRS) studies suggest that there may be elevated levels of the acetylcholine precursor choline in orbitofrontal cortex and other brain regions of individuals with depression (119, 120). The nicotinic receptor blocker mecamylamine has also recently been shown to have some antidepressant properties (42, 121).

It is important to note that antidepressants can effect neural response to injury and repair. For example several recent reports have suggested that antidepressants may have neurotrophic effects including facilitating regeneration of catecholamine terminals in cortical and hippocampal regions (42, 122, 123).

*Treatment* With respect to treatment of depression after TBI, there is a lack of good data. A brief selective review of this literature is provided (see Silver and Arciniegas, Chapter 55 for detailed review). Several papers address the use of tricyclic antidepressants although this is a relatively old literature and the results are somewhat conflicting. Wroblewski and colleagues (124) reported a small randomized, placebo-controlled prospective study, in which 10 individuals with severe TBI and depression were given placebo and desipramine in a crossover fashion. Desipramine was found to be more effective than placebo. Dinan and Mobayed (125) in a cohort study of 13 patients with mild TBI matched with 13 depressed patients without brain injury found amitriptyline to be less effective in the TBI group. Saran (126) using amitriptyline in an open label design found less reduction in depression scores in a mild TBI group than a non-injured group. Significant methodological issues limit the strength of the evidence from all three of the above studies.

A large number of case series and case reports address the treatment of depression after TBI with a variety of

other agents. However methodological problems such as the use of mixed populations (e.g. stroke, penetrating brain injury, TBI, epilepsy) (127, 128), absence of clear diagnostic criteria (127, 129–131), absence of validated outcome measures (129, 130, 131–133), or the use of more than one intervention at a time, limit the conclusions that can be drawn from many of these reports.

Several similar reports have addressed the use of selective serotonin re-uptake inhibitors in this population, but again basic methodological flaws, and small numbers make it difficult to draw conclusions from these papers.

Overall several important points can be made with respect to depression after TBI. The brain regions and circuitry implicated in the genesis of depression overlap to a great extent with those regions at greatest risk for damage in the typical TBI. Furthermore, the major neurotransmitter systems felt to play key modulatory roles in the regulation of mood and affect are the same as those known to be altered by TBI (ie adrenergic, dopaminergic, cholinergic, and serotonergic systems). When one considers the additional roles of stress, loss, social isolation, and other common psychosocial insults common in TBI, it is surprising that the frequency of depression following TBI is not higher.

### MANIC SYNDROMES

Mania is characterized by episodes of sustained (longer than one week) changes in mood (euphoria or irritability) and increased psychomotor activity. It may be associated with increased energy, decreased need for sleep, and a penchant for dangerous behavior (reckless activities, increased spending, increased sexual activity). Some manic episodes can be accompanied by psychotic symptoms such as grandiose delusions or thought process disturbances such as loosened associations or flight of ideas. Mania is a well-described complication of many disorders of the CNS including TBI (134, 135). Robinson et al. (134) found 6 of 66 (9%) carefully characterized TBI patients developed manic episodes. In these patients mania was not associated with severity of injury, post-traumatic epilepsy, family or past personal history of mania. It was associated with lesions in the temporal and orbitofrontal cortices. Shukla et al. (136) reported on 20 individuals with TBI and mania and found that nine of their patients had epileptogenic activity on EEG. Irritable mood not euphoria was more commonly observed. Van Reekum et al. (13) reviewed the literature and suggested that TBI was associated with a five-fold increase in relative risk of developing bipolar disorder relative to base rates in the population. The role of genetic loading in the etiology of mania after TBI is not clear. For example Malaspina et al. (17) did not find an

increase in exposure to TBI in her large bipolar pedigree study.

A variety of other small series and case reports suggest that mania can be seen in association with all injury severities including some cases with brief or no documented loss of consciousness (133, 137–139). The full array of phenomenologic variants of mania can be seen including a bipolar course, rapid cycling, and triggering of manic episodes by antidepressant medications (132, 136, 138, 140, 141).

It is difficult to determine the exact role that profile of injury plays in mania as the underlying circuitry of this disorder is less well established than that for depression. In mania occurring after CNS disorders (not solely TBI) there is a marked preponderance of right fronto-temporal and basal ganglia injury (5, 134, 142).

*Treatment* Although there are many case reports and small series of TBI-related manic syndromes in the literature there are no systematic studies of this issue that one can use to inform treatment. Even the case series and case reports available do not give sufficient data to allow firm conclusions about treatment response. However the impression from this literature and clinical experience suggests that the same agents used in idiopathic bipolar disorder can be effective in TBI-related manic episodes. Thus the usual approach is to control acute manic episodes with an antipsychotic agent such as risperidone, olanzapine, or haloperidol while starting an anticycling agent such as valproic acid or lithium for longer-term prophylaxis of the illness.

### PSYCHOTIC SYNDROMES

The term psychosis refers to a cluster of symptoms, which includes problems in both thought content and thought process. Delusions and hallucinations typically characterize disorders of thought content. Alterations in the structure and flow of speech and language such as loosening of associations, flight of ideas, thought blocking, and production of nonsense words or neologisms, are characteristic of disordered thought process. Psychosis is often equated with schizophrenia, but is more accurately viewed as a syndromic manifestation of many neuropsychiatric conditions, including depression, bipolar affective disorder, delirium, and dementia, to name a few.

Although psychosis is a relatively rare complication of TBI, it does occur more frequently than in the general population. It is a good example of a low frequency, high impact complication of TBI, causing enormous distress to individuals and their caregivers. There are several contexts in which psychotic syndromes following TBI can occur including during the period of post-traumatic amnesia, as a complication of post-traumatic epilepsy, in

the context of TBI-related mood disorders, or associated with a chronic, schizophrenia-like syndrome. It is necessary to distinguish these different contexts, in so far as it is possible, to guide appropriate interventions (143, 144).

Relatively few studies directly address the association and causal connections between TBI and psychosis. Davison and Bagley (145) summarized the results of eight long-term (15 to 20 years) follow-up studies of individuals with brain injuries published between 1917 and 1960. Across these studies, the percentage of TBI patients developing a schizophrenia-like psychosis varies from 0.7% to 9.8%, suggesting an observed incidence of schizophrenia-like psychosis that is 2 to 3 times greater than that expected by chance in the TBI population. Van Reekum et al. (13) reviewed the literature and found a more modest relative risk associated with TBI. The role of genetic vulnerability is also not clear. Davison and Bagley found no evidence of increased genetic loading for schizophrenia in TBI patients who developed psychotic symptoms. Malaspina and colleagues (17) however studied 1830 individuals who were first-degree relatives of people with schizophrenia or bipolar disorder, looking for a relationship between these illnesses and TBI. Compared to other first-degree relatives with similar genetic vulnerabilities, those with a history of TBI were at significantly greater risk to develop schizophrenia. The authors propose a synergistic effect between TBI and genetic risk in families with two or more members with schizophrenia.

Based on the studies to date, it seems reasonable to conclude that psychotic disorders do occur in individuals with a TBI at rates greater than in the non-injured population. The more severe the injury, the greater is the likelihood of psychosis. Psychotic syndromes may occur soon after the TBI, or after a delay of months to many years (see Table 45-3). In cases with delayed onset, the injury is almost certainly not the only etiologic factor, although it is interesting to note the high rate of previous TBI in patients with schizophrenia. Furthermore, it appears that TBI can interact with genetic vulnerability

to greatly increase the risk of developing illnesses such as schizophrenia.

As noted, psychotic symptoms can occur in the context of a seizure disorder, a relatively common complication of TBI. A relationship between seizures and mental disorders, particularly psychotic syndromes, has been commented on for centuries (146) and is the subject of a somewhat confusing literature. In a comprehensive review of studies looking at the prevalence of psychosis in epileptic populations, McKenna and colleagues (147) found prevalence rates ranging from 0% to 27% in small clinic-based studies and rates of 2.8% and 3.2% in larger surveys of patients attending epilepsy clinics. Two large-scale Scandinavian community surveys of individuals with epilepsy found prevalence rates for psychosis of 2% (148) and 7.1% (149), both of which are higher than prevalence rates in individuals without epilepsy.

Epileptic psychosis is overwhelmingly associated with complex partial seizures, occurring four to 12 times more frequently in temporal lobe epilepsy than in other types of epilepsy. Psychotic syndromes are most likely to occur in conjunction with left-sided temporal lobe lesions (150–153). This is particularly the case for schizophrenia-like syndromes and paranoid syndrome.

Psychotic syndromes associated with posttraumatic epilepsy can occur predominantly in the peri-ictal period (either during seizures or in the immediate post-ictal period), or inter-ictally, in which case the psychotic symptoms are more commonly chronic rather than episodic (154). Most commonly seen is a post-ictal acute confusional state characterized by generalized confusion, fluctuating sensorium, agitation, hallucinations, and delusions, which is similar to the posttraumatic delirium described above. This condition generally resolves within a few hours of the seizure, although rarely it may persist for several days.

Less commonly psychotic symptoms occur as part of the seizure ictus. The clinical picture is one of paroxysmal onset of psychotic symptoms which can include auditory, visual or somatosensory hallucinations, delusions

**TABLE 45-3**  
*Interval of Injury to Development of Psychosis in Selected Studies*

STUDY	SAMPLE	LATENCY
Achte et al. 1969, 1991. (Psychopath 24:309–315)	WWII veterans, mainly penetrating TBI	2 days to 48 yrs, 42% occurring 10 yrs after
Fujii and Ahmed, 1996 (Neuropsychiatry, Neuropsych, Beh Neurol. 9:133–138)	State hospital sample	3 mos – 19 yrs, mean of 5.9 yrs
Feinstein and Ron 1998 (J Neuropsychiatry 10:448–452)	44 subjects with psychosis after neurological disorders	0–54 yrs, mean of 11.7 yrs

(often paranoid, grandiose or religious), as well as alterations in thought process (loosened associations, flight of ideas, cognitive disorganization). As with other seizure phenomena, these symptoms usually recede quickly (over several minutes) unless they are associated with repetitive seizures of a more prolonged inter-ictal psychotic syndrome. The most useful clue clinically is the time course of the psychotic symptoms, characterized by the paroxysmal onset, rapid resolution (most commonly), and relative absence of such symptoms in between events (155).

*Relationship of Profile of Injury to Psychosis* A full discussion of the neuroanatomical substrate of schizophrenia and psychotic symptoms is not possible. However a brief overview is instructive. No single brain region has been identified as the site or cause of schizophrenia, rather several brain regions appear to play important roles in the genesis and phenomenology of this disorder. These regions overlap with those vulnerable to injury in the typical TBI. Computed axial tomography (CT) scan and magnetic resonance imaging (MRI) studies of patients with schizophrenia have identified enlarged lateral and third ventricles (156, 157), reduced frontal and temporal lobe volumes (158), reduced thalamic volumes (159), and enlargement of basal ganglia, particularly the caudate and globus pallidus (160–162). Functional imaging studies have also focused on frontal, temporolimbic, and basal ganglia areas. Positron-emission tomography (PET) studies of drug-free schizophrenics have suggested reduced metabolism in the cingulate gyrus and hippocampus, (163, 164) and reduced metabolism in the basal ganglia (165, 166). Some schizophrenic patients have abnormal patterns of frontal activation when engaged in cognitive tasks that require frontal function (163, 166).

Recent neuropathological studies of patients with schizophrenia have suggested abnormalities in regions of the dorsolateral pre-frontal cortex and the hippocampus. Selemon and colleagues (167) reported prefrontal (Brodmann's area 9), as well as more widespread increased neuronal density in association with reduced cortical thickness. They thought this finding might be related to reduction of neuropil. Akbarian and colleagues (168, 169) reported abnormal distribution of nicotinamide adenine dinucleotide phosphate diaphorase-expressing neurons in both dorsolateral prefrontal cortex and temporal cortex. They postulated that these findings were consistent with altered (incomplete) migration of this population of neurons. Furthermore, these cells participate in subsequent guidance of other migrating neurons, pruning, programmed cell death, and overall modulation of proper "connectivity."

The temporal lobes, particularly the left temporal lobe and the hippocampal formation appear to play a role in auditory hallucinations and in delusions of passivity and control. Dysfunction of the prefrontal cortex is also implicated in delusion formation. It is not surprising then

that psychotic syndromes occur with increased frequency in patients after a TBI. There is significant overlap between the regions implicated in the etiology of schizophrenia and its prominent symptoms, and those regions which are commonly affected in TBI, including the frontal lobes (both dorsolateral cortex and orbitofrontal cortex), temporal lobes, basal ganglia, and thalamus. In some respects, it is surprising that psychotic syndromes are not seen more commonly after TBI.

*Treatment Issues* A critical first step in the evaluation and treatment of psychotic symptoms is making an accurate diagnosis and determining the etiology of the psychotic symptoms. This necessitates distinguishing psychotic symptoms from other brain injury-related symptoms such as confabulation, misidentification syndromes, and delusions (170). Once the presence of psychotic symptoms has been clearly established, a diligent search for underlying causes is necessary. A history of any earlier psychiatric illness must be aggressively sought. A positive family history of psychiatric illness can give valuable clues about the patient's diagnosis. It is important to determine whether the psychotic symptoms are related to a post-traumatic seizure disorder, a mood disorder (either depression or mania with psychotic features), concurrent or past substance abuse, or a manifestation of a schizophrenia-like disorder.

Treatment approaches follow logically from this differential diagnosis. Seizure-related symptoms are best managed with adjustment of the anticonvulsant regimen or consideration of surgical approaches in refractory cases. Mood disorders are best treated with antidepressants or anti-cycling agents (12, 171–173). Single agents should be tried initially, but a combination of drugs may be necessary. Antipsychotic agents may be needed in the initial phases of treatment of a mood disorder with psychotic features, but these should be tapered and discontinued once the mood disturbance has been successfully treated. Treatment of associated substance abuse can be very difficult, but must be attempted (174).

Should these initial treatments efforts fail, or when a psychotic syndrome is the primary psychopathology (i.e., the patient appears to have a schizophrenia-like disorder), then antipsychotic agents must be used. There are several potential problems with the use of these agents. It is therefore critical that they be used sparingly and for the treatment of true psychotic symptoms, not for the management of nonspecific agitation. Problems with motor function, gait, arousal, and speed of information processing are common in brain-injured patients and can be exacerbated by the sedation, psychomotor slowing, parkinsonism, and anticholinergic side effects associated with the common antipsychotic agents. TBI may also increase the likelihood of tardive dyskinesia (175). Clinicians often report this increased sensitivity to side effects of psychotropics, although there is little systematic evidence

to confirm these observations (5, 12, 171, 173, 176). It is prudent to start with one third to one half of the usual starting doses and to lengthen the interval between dosage increases. Newburn (177) reviewed the pharmacotherapy of psychiatric disorders associated with TBI, advising caution with drugs having prominent anticholinergic, antihistaminic, or antidopaminergic effects because of risk of adverse effects on cognition. Also, traditional antipsychotic drugs should be cautiously used because they might decrease synaptic plasticity.

*Atypical Antipsychotics* Atypical antipsychotic drugs have emerged as first line drugs for treatment of psychotic disorders. They are also being used with increasing frequency to treat ill-defined anxiety syndromes and mood disorders. Unless there is evidence that psychotic signs and symptoms are a direct result of some other treatable condition, such as cerebral dysrhythmia, one of these drugs should be employed. Six such drugs are currently available: clozapine, risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone. These drugs offer two main advantages over conventional neuroleptic drugs. They have greater efficacy, especially in decreasing negative as well as positive symptoms of schizophrenia, and in decreasing agitation and aggression. The latter effect can be of particular benefit in some individuals with TBI. Most importantly, the atypical antipsychotics carry significantly less risk of causing extrapyramidal symptoms (EPS) and tardive dyskinesia. Like all drugs with antipsychotic activity, the atypicals have some blocking effect on dopamine-2 ( $D_2$ ) receptors, but proportionally less so than conventional drugs. The atypical class also shows a preference for limbic  $D_2$  receptors with minimal nigrostriatal effects, and thus less risk of EPS. Affinity for 5-HT<sub>2A</sub> receptors is thought to also contribute to decreased EPS risk (178).

Clozapine is considered the most potent and effective of the atypical antipsychotic agents. However, it is also associated with the most side effects, including a heightened risk of agranulocytosis. Clozapine also has the most prominent anticholinergic effects and can cause orthostatic hypotension (178, 179). Drooling and sedation can be distressing problems with clozapine. Weight gain can occur with all of the atypicals but is probably more likely with clozapine and olanzapine. Clozapine carries greater risk of causing seizures, which is a consideration in treating patients with a history of brain injury. Due to this side effect profile, clozapine will not usually be the first of the atypicals to try. It is rational to try at least two of the other atypical antipsychotic drugs before beginning a clozapine trial. Among the other four, none shows clearly superior efficacy. A particular patient's history of previous response, minimizing certain side effects, and the clinician's familiarity with one drug or another all affect choice of drug. In some instances, one might wish to use a side effect, such as sedation or tendency to cause weight gain to advantage.

A variety of case reports and small case series that suggest most of the atypical antipsychotics can be used to effectively treat psychosis resulting from TBI (131, 180–183), though there are no randomized controlled trials to date. For example Butler (180) reported persecutory and nihilistic delusions, Capgras delusions, and depersonalization in a 17-year-old man after TBI. The delusions completely resolved within 2 weeks of beginning treatment with olanzapine, 5 mg daily. Feinberg and colleagues (181) reported a 61-year-old man who developed misidentification delusions of the Fregoli type after suffering right frontal and left temporoparietal contusions. Umansky and Geller (182) reported successful treatment with olanzapine of psychosis and affective disturbance after severe TBI with frontal lobe injury in a 42-year-old man. Laddomada and colleagues (183) reported successful treatment of psychosis after TBI with clozapine in a 25-year-old man. Previous treatment with clonazepam and carbamazepine had not helped.

Thus, psychosis in a brain-injured patient can be successfully treated, but requires a thorough diagnostic assessment to discern the underlying cause, and the rational pharmacotherapeutic approach that follows logically from this diagnostic process. Medication approaches must be adjusted for the particular characteristics and vulnerabilities of the patient with a TBI.

## ANXIETY DISORDERS

Anxiety is a common complaint in injured and non-injured populations alike. There are several different patterns of anxiety including generalized anxiety, panic disorder, phobic disorders, obsessive-compulsive disorder, and post-traumatic stress disorder. There are relatively few studies however addressing the incidence of these disorders after TBI and even fewer studies addressing treatment options (see (184) for review).

*Generalized Anxiety Disorder (GAD)* Van Reekum et al. (13) reported a 2.3 fold increase in relative risk for GAD based on five studies that met their inclusion criteria. For example in a study by Fann et al. (7), 24% of their sample (the majority of whom had mild TBI) evaluated 2–3 years after injury met criteria for generalized anxiety disorder. Many had co-morbid depression and many had symptoms that pre-dated their TBI. Robinson and Jorge (185) also found high rates of co-morbid anxiety and depression. 76% of their sample of depressed TBI patients also met criteria for generalized anxiety disorder (GAD). 22% of the non-depressed group also met GAD criteria.

Hibbard et al. (15) also found high rates of several different anxiety disorders (PTSD, 19%; obsessive-compulsive disorder, 15%; panic disorder, 14%; GAD, 9%) in their sample of 100 individuals with mixed injury



severity studied an average of 8 years after injury. Deb et al. (107) found a high rate of panic disorder (7%) but no change in rates for GAD or obsessive compulsive disorder relative to the general population.

The question of anxiety symptoms and their link to post-concussive symptoms is an important one. There is a significant overlap between many postconcussive symptoms and core symptoms in generalized anxiety disorder. Thus, many patients endorse complaints of headache, dizziness, blurred vision, irritability, and sensitivity to noise or light after mild brain injury (56, 186, 187). It is less clear how many patients actually experience anxiety and how many have diagnosable anxiety disorders. Although 55% of Dikmen's group (186) of 20 patients with mild brain injury complained of subjective anxiety, 45% of the matched control subjects had similar complaints (a statistically nonsignificant difference). Schoenhuber and Gentilini (188) were unable to find a significant difference in mean anxiety scores in their study of 35 patients with mild brain injury and matched control subjects.

*Obsessive-Compulsive Disorder* Three studies (13, 15, 189) assessed their TBI populations for obsessive-compulsive disorder. As pointed out by Van Reekum et al. (13) these studies represent a combined sample of 282 subjects followed for a maximum of 7.5 years. 6.4% had obsessive compulsive disorder which represents about a 2-fold increase in relative risk compared to the general population.

*Post-Traumatic Stress Disorder (PTSD)* There is an increasing awareness of the relationship between PTSD and brain injury. Initially it was assumed that the presence of post-traumatic amnesia prevented the development of PTSD by preventing the formation of what was felt to be a core component of the syndrome – the exquisitely vivid memories and re-experiencing of the traumatic life-threatening event. In fact there is evidence that individuals with loss of consciousness, particularly 15 minutes or more do have reduced rates of PTSD (184, 190, 191). However this is by no means an absolute rule. McMillan (192) reported on 10 individuals who met criteria for PTSD despite amnesia for the traumatic event and several others have reported similar findings (193–195). However it is more common to see PTSD and PTSD-like syndromes in individuals with at least partial recall of the events. Patients with a history of mild brain injury seem to manifest signs and symptoms suggestive of PTSD fairly commonly. Symptoms may include sleep disturbance, recurrent nightmares, exaggerated startle responses, daytime flashbacks, and avoidant behaviors such as refusing to drive or leave home. Driving phobias may become prominent. Lishman (1), in his review of the psychiatric sequelae of brain injury, refers to PTSD-like symptoms, concluding that “the circumstances of the accident may recur vividly in dreams, maintain states of

anxiety, or become the focus for obsessional rumination or conversion hysteria” (p. 306). McMillan (196) described PTSD symptoms in a woman with a severe brain injury despite amnesia for the event itself and a PTA of approximately 6 weeks.

Bryant and Harvey have reported a series of studies of individuals hospitalized after motor vehicle accidents, some with and some without TBI (usually mild TBI). They have shown that rates of acute stress disorder 1 month after an accident are comparable in the two groups, and that acute stress disorder is a good predictor of those who go on to develop PTSD 6 months after injury (197–199). For example, they studied 46 individuals admitted to a hospital after an MTBI (LOC with PTA <24 hours) and 59 survivors of motor vehicle accidents without evidence of TBI 6 months after their accidents (194, 200). Twenty percent of the TBI group and 25% of the non-TBI group had PTSD. The TBI group had more postconcussive symptoms than did the non-TBI group. Furthermore, the TBI group with PTSD was significantly more symptomatic than the TBI without PTSD group. This suggests that, like other psychiatric disorders such as depression, PTSD can amplify postconcussive symptoms after an MTBI and complicate recovery. In a sample of individuals with mild TBI (LOC <15 minutes), Mayou et al. (2000) found that almost half (48%) of those with definite loss of consciousness had PTSD 3 months after injury, and one-third of their subjects with MTBI had PTSD 1 year after injury. Although it might at first seem strange that those with LOC could develop PTSD with intrusive memories, it has been suggested that the intrusive memories are of events immediately before or after the accident, or there may be patchy amnesia with some islands of preserved memory.

Warden et al. suggest that a PTSD-like syndrome does occur after TBI but that the phenomenology may be different from that seen in individuals without TBI. They studied 47 members of the Armed Forces who sustained moderate to severe TBI. Using the strict definition of PTSD defined in DSM-III-R, none of the individuals met full criteria for PTSD. However when the re-experiencing criteria was dropped under the assumption that the traumatic amnesia would make this symptoms less likely, 13% met these revised criteria. This study is particularly instructive in that it raises the issue of sub-syndromal levels of PTSD. As Warden et al. described, patients who do not meet formal criteria for PTSD yet manifest many of the core symptoms (apart from the re-experiencing) are commonly seen. This highlights the fact that clinicians must be aware of the profile of injury through which psychiatric symptoms will be expressed following a TBI. In this case the injury associated memory loss alters one of the key components of PTSD seen in the non-injured population, and yet the rest of the core symptoms are present, can cause enormous disability, and

need aggressive treatment. Failure to appreciate this altered clinical phenomenology on the one hand, or excessively rigid reliance on DSM criteria developed without the TBI population in mind can lead the clinician astray.

Thus it seems that GAD, panic disorder, obsessive-compulsive disorder, and PTSD do occur at increased rates in individuals with TBI compared to the general population. As with the other psychiatric disorders discussed, the phenomenology of the disorders may be altered by the “filter” through which the symptoms are expressed.

*Treatment* Very little information is available with respect to treatment of these disorders in individuals with TBI (see Chapter 55). Warden and Labbate (184) suggest that education and cognitive-behavioral therapy have an important role in treatment. There are no systematic medication trials. Thus the usual approach is to follow the same treatment algorithm for anxiety disorders in the non-injured population. Selective serotonin re-uptake inhibitors such as sertraline or citalopram are useful first-line agents for both GAD and obsessive-compulsive disorder, and arguably for panic disorder and PTSD. Benzodiazepines can be useful but are often second line agents due to their effects on cognition and the high rate of substance abuse disorders in the TBI population. Atypical antipsychotics such as risperidone, quetiapine, and olanzapine are increasingly being used to treat anxiety. However these should be third line agents due to the potential for weight gain or full metabolic syndrome and the less likely but real concern for the development of tardive dyskinesia. Aripiprazole and ziprasidone may be better choices in individuals who are already overweight or at risk for metabolic syndrome. Buspirone can also be of benefit to some individuals. It is important to give this agent a several week trial before assessing efficacy as it takes this long to have an effect.

## SUBSTANCE ABUSE

Use of alcohol and other substances can play an important role in TBI including etiology, neuropathophysiology, recovery, and functional outcome (see Chapter 40). For example about half of all traumatic brain injuries involve the use of alcohol, and about one half of these individuals are intoxicated at the time of injury (174). The majority of these individuals have pre-injury patterns suggestive of addictive drinking (alcohol dependence)(201). In fact alcohol use is the single greatest risk factor for TBI, and TBI is often an irreversible consequence of alcohol and drug abuse (201). The presence of alcohol at the time of injury predicts longer durations of unconsciousness (202), increased challenging behaviors during the acute hospitalization (203), cognitive outcome (204) and overall outcome including mortality(205).

Individuals with pre-injury substance abuse problems often continue to struggle with these issues after their injury. Ashman et al. (109) found that their TBI population had an almost 2-fold increased rate of substance use disorders (drug/alcohol abuse/dependency) relative to the general population (32% vs. 17%) *prior* to injury. Subsequent to injury the rates went down initially probably reflecting enforced abstinence related to hospitalization and rehabilitation stays. However by the third assessment point the rate was identical to that seen in the general population (17%). In an earlier study of 100 individuals studied at least one year (mean 7.6 years) after injury, 28% of the sample struggled with substance use disorders (15).

*Treatment* A full discussion of this topic can be found in Chapter 40. In the acute hospitalization period it is important to be alert to the potential for substance withdrawal syndromes. Treatment of withdrawal from alcohol and drugs in addicted patients with TBI are similar to those employed in patients without TBI, with some important exceptions. The identification of alcohol and drug intoxication and withdrawal follows the general principles of pharmacological dependence. The use of blood and urine toxicology is important to identify the presence and levels of alcohol and drugs for assessment of intoxication and anticipation of withdrawal. The use of vital signs, particularly blood pressure, pulse, and temperature, are critical in determining the presence and severity of the withdrawal state (206).

After the acute and sub-acute rehabilitation phase, it is often desirable to prescribe aggressive treatment for substance abuse problems that appear likely to persist. However there are a variety of issues that complicate this process in individuals with TBI. Although counseling and the use of group therapy and 12-step recovery models remain the mainstay of treatment (see (201) for review) the cognitive deficits of many with TBI makes these interventions more difficult in that there is often relatively little or no carry-over of issues discussed from one session to the next.

There is often a significant problem with denial. Disorders of substance use are frequently associated with a resistance or psychological denial with respect to the impact that the substance use has on an individual's life. This can be greatly compounded by the deficits of awareness that were described earlier (see (78)). Thus there is a double denial (denial of substance abuse and TBI-related deficits) that can hamper establishment of a therapeutic alliance around the need for treatment.

There are also difficulties related to the usual treatment settings. Individuals with TBI can find group meetings (e.g. AA or NA meetings) over stimulating. This can result in further difficulties processing the informational content of the meetings. Furthermore the difficulties in social comportment described earlier can become quite apparent in group settings and when individuals are over

stimulated. This can result in the individual being asked to leave or not being welcome at future meetings. There can be a culture within groups that discourages or downplays the need for psychotropic medications and this can be detrimental to individuals who are already wavering in their commitment to medication compliance especially if they are not convinced that they have a problem in need of treatment.

Despite the above difficulties, the tried and true interventions remain the cornerstone of treatment. Thus additional supports are needed to enhance their efficacy in individuals with TBI. Basic principles used in working with individuals with TBI work in addiction treatment as well. Individuals will do better with concrete and structured settings. Whenever possible programs should be geared to the cognitive level of the individual. When this is not possible the use of a buddy system to help to translate or operationalize the information from individual or group sessions to real life can be effective. It is important for the treatment team to have a thorough understanding of both addiction and TBI to provide a consistent, cogent, and effective treatment plan (201).

Techniques such as keeping treatment interventions simple, focused, and concrete are critical in both patient populations (201). Clinicians may find a need to be more directive and supportive than they are accustomed to with other patient populations (174). Redirection using appropriate cues and reinforcers is often needed more than in other populations. It is important to teach substance use prevention skills that can be used in more than one life setting to maximize generalizability. As noted it is important to never assume understanding or memory of content from previous session. This requires the therapist to be redundant both within and between sessions. It can be helpful to summarize previous progress and then restate where the previous meeting left off (i.e. be redundant) (174, 201).

### Dementia

Dementia is defined in the DSM as a syndrome characterized by impairment in memory and at least one other domain of higher cognitive function (“memory plus”) that is of sufficient severity to interfere with social and or occupational function. Although progression is often inferred this need not be the case. Thus many individuals with TBI who have significant impairments in memory and executive function meet this definition of dementia. However the larger issue is whether exposure to a TBI increases the risk of a progressive dementing disorder such as Alzheimer’s dementia (SDAT) later in life (see Chapter 32 for discussion of the full scope of late complications of TBI). At this time it is not possible to say definitively whether TBI, particularly mild TBI is a risk factor for Alzheimer’s disease. This topic has been recently reviewed

by Jellinger (207) who concluded that both SDAT and TBI are associated with abnormalities in amyloid and tau protein deposition and that several epidemiological studies have suggested either that SDAT occurs with increased frequency in individuals with TBI or that the age of onset of SDAT is reduced after TBI relative to non-injured controls. Furthermore the possibility exists that the two conditions share common genetic vulnerabilities with respect to polymorphisms in the apolipoprotein E (ApoE) gene.

ApoE is a complex glycolipoprotein that facilitates the uptake, transport, and distribution of lipids. It appears to play an important role in neuronal repair and plasticity after injury (208). A four exon gene codes for ApoE on chromosome 19 in humans. There are three major alleles: e2, e3, and e4. These alleles differ in amino acids at positions 112 and 158: e2 (cysteine/cysteine), e3 (cysteine/arginine), and e4 (arginine/arginine). Animal models suggest a link between the e4 allele and increased mortality, extent of damage, and poor repair following trauma (208, 209). The human e4 allele has been associated with a variety of disorders with prominent cognitive dysfunction including normals with memory complaints (210), AD, and poor outcomes in stroke and TBI (208, 211). Several studies have reported that the e4 allele is associated with poor outcomes following TBI, using a variety of measures (212, 213). Crawford et al. (214), for example, found poorer memory performance in their sample of 30 individuals with TBI with at least one e4 allele compared to 80 TBI patients without an e4 allele. Lichtman et al. (215) found lower total functional independence measure scores in seven e4(+) patients with TBI compared to the 24 individuals with TBI but without an e4 allele. Friedman et al. (216) found a significantly higher percentage of poor outcome indicators both acutely (prolonged loss of consciousness), and at 6–8 months after injury (significant dysarthria, global functional outcome rating) in 27 individuals with TBI and the e4 allele compared to 42 individuals with TBI but without an e4 allele. Liberman et al. (217) found lower cognitive performance on several cognitive measures at 3 weeks but not 6 weeks after injury in the e4(+) patients. In a recent 30 year follow up study of individuals with TBI Koponen et al. (218) found that 6 of 19 e4 (+) individuals had definite or probable SDAT, whereas none of the 41 e4 (–) individuals had developed SDAT.

The mechanism by which the e4 allele exerts its negative effect is unclear. ApoE4 shows an increased affinity for beta amyloid and thus an increased propensity to promote aggregation of beta amyloid (216). Rather than an active detrimental effect, it may be that the ApoE4 is less effective than ApoE3 in promoting neuronal repair, and neuritic growth and branching. There may be a cholinergic link between the ApoE and cognitive impairment (see (219)). In AD, the degree of reduction of choline acetyl transferase, one of the markers for the disease, is correlated with the “dose” of e4 (208). Parasuraman et al. (220) have

argued based on accumulated neuropsychological, electrophysiological, and neuroimaging evidence that the cognitive effects of the e4 allele are mediated through reduced cholinergic input to posterior parietal systems regulating selective attention.

Thus similarities in neuropathological findings and response to neurotrauma, genetic vulnerabilities with respect to apolipoprotein E, and some (though not all) epidemiological studies suggest that there is a link between TBI and subsequent development of SDAT. However further clarification is needed. From a clinical standpoint the important issue is the stability of cognitive deficits over time. Any individual who has had stable cognitive function after the period of spontaneous recovery that begins to show evidence of cognitive decline must have an aggressive evaluation for the underlying cause as this is not the typical course following TBI.

## NEUROPSYCHIATRIC ASSESSMENT

It is clear from the above that a careful assessment of neurobehavioral concerns should be an important component of the evaluation and rehabilitation of individuals with TBI. A full discussion of all the dimensions of a neuropsychiatric assessment will not be attempted (see (221) for review). However it is worth highlighting several points.

*Need for Multiple Sources of Information* The cognitive deficits that frequently accompany a TBI alter the neuropsychiatric assessment, particularly the history taking. The presence of short-term memory deficits, problems with sequencing events in time, and difficulties with self-monitoring and self-awareness can make it very challenging for an individual to give a clear and consistent history. This puts the onus on the clinician to identify other sources of information (family members, friends, employers, primary medical/school/vocational records) that can help clarify the history and current clinical picture. The clinician must also obtain permission from the injured individual and work hard to explain the need for others to be involved in the treatment as observers and sources of critical information.

*Assessment of Pre-Injury Baseline* Assessment of the effects of an injury must start with a thorough understanding of what the individual was like prior to the injury. Absent such information there is a significant risk of mis-attributing life-long traits, characteristics, and behaviors to the brain injury. The following domains should be carefully explored and efforts made to gain primary records and reliable history with respect to:

- *Medical history*
- *Neurobehavioral traits and characteristics* (e.g. history of psychiatric illness)

- *Intellectual capacity* (indicators include educational history, vocational history, parental education)
- *Functional performance* (profile of personal, professional, and vocational accomplishments)
- *Personality style* (indicators include patterns of coping with stress, stability of key relationships)

Proper information on the above domains helps to paint a picture of life before the injury. Ideally such information is obtained shortly after the injury. The more time that passes from the point of injury, the greater the tendency to (mis) attribute more issues and life events to the injury. It is important to not simply take the word of injured individuals and their family/caregivers that “he was always perfectly normal” but make efforts to get primary documentation, not just “hearsay”.

*Assessment of Post-Injury Changes* Once the baseline picture is complete, the clinician is positioned to accurately assess the changes that have occurred since the time of the injury. It is important to carefully review the functional domains that are frequently affected by injury including cognition, personality, mood regulation, speech/language, mobility, and higher order domains such as vocational performance, major role performance within the family or equivalent context. It can be helpful to use standardized assessment scales and tools that serve to sample the full array of common problems such as the Neurobehavioral Rating Scale-revised (222) or the Neuropsychiatric Inventory (223). Alternatively one can use scales and instruments that offer a more detailed approach to a given problem area specific to the individual being assessed such as the Overt Aggression Scale (224) or Apathy Evaluation Scale (225). For bedside assessment of cognition it is helpful to supplement a standardized instrument such as the Mini Mental Status Exam (226) with something that helps to assess frontal executive functions such as the Frontal Assessment Battery or the Behavior Rating Inventory of Executive Function (BRIEF, (227, 228)), (see Table 45-4).

*Attribution of Etiology* It is important to emphasize that temporal association does not guarantee causality. There are several ways that neurobehavioral change can be associated with brain injury. Change may be a direct effect of the insult to neural tissue with subsequent disruption of the functions sub-served by the damaged tissue. For this to be properly assessed requires accurate, sometimes fine-grained knowledge of the profile of regional brain injury and the relationship of the related circuitry to the functional change in question (the “neural component”).

Alternatively the change may reflect the development of a new illness or disorder that is the driving force behind the behavioral change. For example an individual may develop various endocrine complications of their brain injury related to pituitary damage, chronic pain

**TABLE 45-4**  
*NeuroBehavioral Rating Instruments Useful in TBI*

<b>NAME OF INSTRUMENT</b>	<b>COMMENTS</b>	<b>FORMAT</b>	<b>NUMBER OF ITEMS</b>	<b>APPROXIMATE TIME TO ADMINISTER</b>	<b>OUTPUT</b>
<b><i>BEDSIDE MEASURES OF COGNITION</i></b>					
Mini-Mental Status Exam (226)	Not a good measure of frontal executive functions	Rater administered	30	5 minutes	Score range to 30
Frontal Assessment Battery (230)	Good measure of executive function	Rater Administered	6	5–10 minutes	Score range to 18
BRIEF-A (228)	Good measure of executive function	Self-report or Family/caregiver report	75	10–15 minutes	Total and subscales
<b><i>MEASURES OF SPECIFIC BEHAVIORS</i></b>					
Beck Depression Inventory (231)	Requires self-awareness, ability to read, some memory skills	Self-report	21	5 minutes	Normal score less than 10
Spielberger State Trait Anxiety Inventory (232)	Measures both current (state) and trait anxiety. Requires self-awareness, ability to read, some memory skills	Self-report	40	5 minutes	Scores range from 20 to 80
Overt Aggression Scale (224)	Good coverage of common aggressive behaviors	Rater administered	16	5 minutes	Total and domain scores
Apathy Evaluation Scale (225)	Good coverage of common symptoms suggestive of apathy	Self-report and informant	18	10 minutes	Total score
Scale to Assess Unawareness of Mental Disorders (233)	Assesses patient view of whether an individual is aware of problems in personality and behavior	Rater administered	20	10 minutes	Assess awareness and attribution of specific psychotic symptoms
PCL-S (234)	Assesses symptoms commonly associated with PTSD	Self-report	17	5–10 minutes	Total scores
<b><i>SURVEYS OF BEHAVIOR</i></b>					
Neuropsychiatric Inventory (223)	Excellent coverage of common symptoms. Somewhat lengthy	Rater administered	91	10–20 minutes	Total score and 12 domain scores
Neurobehavioral Rating Scale – Revised (222)	Excellent coverage of common symptoms	Rater administered	57	15 minutes	Total score, domain scores

from orthopedic injuries, or depression that more reasonably explains the behaviors in question (the “biological component”). It is equally plausible that behavioral change could be caused by the meaning of the accident or injury, a reaction to a loss of self-esteem due to disfiguring injury, loss of mobility, or unemployment (the “psychological component”). Finally, changes in environment such as living situation, change in caregivers, or change in routine or flow of daily life can have an enormous impact on the behavior and adaptation of an individual with brain injury (the “social component”).

*Formulation and Interpretation* All of the above factors can reasonably be attributed to the event of the injury. For example the individual would not have endocrine abnormalities save for the injury-related pituitary damage, or may well have not developed depression absent the injury. However the degree of linkage to neural tissue damage varies across these factors. An individual showing new, aggressive outbursts associated with a change in residential care providers may be better served by working to further train the residential provider rather than by the aggressive use of medications. On the other hand if this patient has clear evidence of orbitofrontal damage, it may be that their threshold for tolerating frustration is so lowered that treatment will require both medication approaches and environmental manipulation.

The proper assessment and formulation of the relative weighting or contribution of each of these factors to the genesis of the challenging behaviors frames what can be termed a neurobiopsychosocial paradigm. It differs from more traditional psychiatric assessments with respect to the critical importance placed on understanding the profile of regional brain injury, and the array of complex behavioral circuitry that this profile would reasonably disrupt. Thus the work of the neuropsychiatric assessment can be summarized as the process of matching the profile of brain injury with the changes that have occurred in cognition, behavior, and overall function, and gauging the “goodness of fit” between predicted and actual outcomes. This is followed by an interpretative process whereby the clinician assigns relative weights to the various contributions made by the neural, biological, psychological, and social components. Treatment interventions should flow logically from this formulation. It is important to point out that even experienced clinicians can make mistakes in this process due to the complexity of clinical presentations and the incomplete data available. Thus the final critical component to this process is the regular re-evaluation of intervention efficacy. Essentially each formulation should be hypothesis driven and each intervention flow logically and in an empirically testable fashion (e.g. “I believe the increase in aggression is due to depression, thus I will prescribe antidepressants”). Poor or incomplete response to the

intervention should prompt a re-evaluation and formulation of a new and testable hypothesis. It is acceptable to be wrong, it is not acceptable to engage in sloppy thinking.

## PRINCIPLES IN TREATMENT

A detailed approach to specific syndromes and disorders can be found in Chapter 55 (Silver and Arciniegas), and Chapter 56 (Arciniegas and Silver). However several general treatment principles are worth emphasizing.

*Variability in Presentation* It is important to be aware that the presentation of psychiatric syndromes in individuals with TBI may differ from the presentation in the non-injured population. In general, the more mild the TBI, the more similar the presentation is. However special challenges arise in more severely injured individuals with cognitive, motor, and speech/language deficits. There are three broad factors that contribute to variability in clinical presentation.

*Mood Instability and Affective Lability* Due to the instability in mood and affect accompanying disruption of the aforementioned frontal-subcortical circuits, it is necessary to pay attention to an extended baseline of behavior. Individuals with TBI are subject to more rapid fluctuation in mood and affect and this overall instability should not be equated with the more sustained alteration in mood that is the hallmark of depression. Attributing internal feelings to external behavior is more difficult due to the frequent presence of pathological or “pseudobulbar” affect (76).

*Alterations in Speech and Language Function* Varying degrees of speech/language impairment are commonly seen following TBI, particularly in individuals with more severe injuries. These changes can range from subtle problems with naming and word finding to global aphasia. Dysarthria and articulation problems can be seen. The ability to modulate the prosody of speech can also be altered (229). This is manifested by difficulties in modulating speech tone, pitch, and amplitude (expressive aprosody), or in decoding and interpreting these components in the speech of others (receptive aprosody). The result of these deficits is an uncoupling of the content or propositional component of speech from the emotional valence and related non-verbal components of language. Patients with receptive dysprosody may have difficulty reading social cues and this may contribute to problems in social comportment. Those with expressive dysprosody may express distressing thought content without seeming to have appropriate accompanying affect (e.g. “I am depressed and suicidal” expressed in a flat monotone without depth of feeling) leading the clinician to be somewhat confused about the clinical significance of what is being expressed.

### *Effects of Associated Neurological Impairments*

One must also consider the effect that injury-related neurological deficits may have on clinical symptoms of psychiatric disorders. For example how will depression be expressed or manifested in non-verbal patients? How will delusions and hallucinations be evident in these same patients? In an individual with quadriplegia, what does manic hyperactivity look like? How will PTSD present in someone with amnesia for the event? Thus the clinician must become adept at envisioning what the psychiatric illness would look like if expressed through the filter of the individual's neurological and functional deficits.

*Effects of Cognitive Impairment* Individuals with poor self-monitoring, impaired memory, distorted sense of time, or time-sequencing deficits will have significant problems presenting an accurate history. The clinician must rely not only on what the individual reports but must strive to get additional information from family/caregivers.

### *Heightened Vulnerability to Medication Side Effects*

Individuals with TBI as well as other neuropsychiatric disorders often manifest an increased sensitivity to medication side effects. This may take several forms. The first is a tendency to develop typical side effects associated with the given medication at a lower than usual dose. The second is a lowered threshold at which the individual develops a delirium or toxic encephalopathy. The third is a worsening of the neurological deficits associated with the TBI. For example it is not uncommon to observe worsening of tremor or gait problems, increased emotional lability, or increased slowing of speed of information processing associated with psychotropic drug use. In other words the very symptoms the clinician is treating may be made worse by the medications prescribed. This highlights the need to take a careful medication history encompassing not only the current medications but medications used in the past as well as the response to those agents. Furthermore it is important to clarify whether a history of "that medicine didn't help" reflects a true lack of response or more a manifestation of the heightened vulnerability to side effects just described.

The above issues contribute to diagnostic and treatment challenges that can be outlined as follows:

- (1) *Atypical Clinical Presentations* – As noted earlier, clinical presentations of common psychiatric disorders may not meet standard diagnostic criteria as outlined in the DSM. Thus it is reasonable to have a "relaxed fit" criteria when approaching diagnoses in individuals with TBI.
- (2) *Trait vs. State Presentations* – It is important to point out that there are two broad factors that contribute to the neurobehavioral sequelae of TBI; the injury induced changes in personality, and the increased rate of psychiatric disorders. A problem arises when the latter presents as a heightening or worsening of the former. For example it is quite common for an individual with TBI to have a baseline of increased irritability or lowered frustration tolerance. It is also quite common for these traits to be exaggerated in the presence of a superimposed episode of depression or mania (or some other psychiatric disorder). If the clinician does not carefully tease out the post-injury baseline and clearly ascertain whether there is a change in the frequency and/or intensity of the challenging behaviors, it is easy to misattribute challenging behavior to a dysexecutive syndrome only, as opposed to a dysexecutive syndrome exacerbated worse by the presence of an Axis I psychiatric disorder.
- (3) *Treat syndromes or disorders not symptoms (diagnosis before treatment)* – It goes without saying that it is best to have a clear sense of what is causing the challenging behavior before designing a treatment plan. Yet many clinicians are inclined to prescribe antipsychotics or SRI's without formulating a hypothesis for what they are treating. This is a symptomatic approach – similar to treating a fever associated with a bacterial infection with acetaminophen but not antibiotics. In the neuropsychiatric arena, the symptomatic approach should be a last resort after having carefully ruled in or out the presence of an Axis I disorder (e.g. depression, mania, psychosis), neurological conditions that would account for the behavior (e.g. complex partial seizures, pain, iatrogenic complications, medication side effects), or factors in the environment that are causing the change in behavioral symptoms. Again it is important to restate that being wrong sometimes is unavoidable, but sloppy diagnostic thinking is avoidable.
- (4) *Role of behavioral metaphors* – There are times, especially when data is difficult to obtain or when the neurological deficits through which challenging behaviors are being expressed are severe, that one is at a loss to account for the etiology of a given behavior or behaviors, and thus not clear about a treatment strategy. A fallback position is to attempt to conceptualize the cluster of behaviors as if they were a particular syndrome or as if they represented what Tariot et al. (235, 236) have termed a "behavioral metaphor". For example an individual expressing increased negativism, loss of interest in activities, and/or self-destructive or self-injurious behavior might be conceptualized as having a depressive syndrome (see Table 45-5) and thus could reasonably be prescribed an antidepressant regimen. An individual with increased irritability, increased arousal and activation, and a significant reduction in sleep might be conceptualized as having an irritable manic-like syndrome and thus be started on an anti-cycling

**TABLE 45-5**  
*Examples of Behavioral Metaphors*

TYPE	BEHAVIOR	INITIAL TREATMENT
Depressive	Negativistic, lack of interest in activities, Weepy, aggressive or self-injurious behavior	SSRI's or other antidepressants
Manic	Increased level of arousal and activity, irritability, decreased need for sleep, increased sexual activity	Mood stabilizers or anti-cycling agents (e.g. anticonvulsants, lithium)
Psychotic	Consistent misinterpretation of environment in a paranoid fashion, apparent response to internal stimuli, aggression that "comes out of nowhere" but may flow out of paranoid misinterpretation of events	Antipsychotics (e.g. low dose risperidone)
Anxiety	Challenging behaviors most apparent in setting of anticipation of events, change in routine, consistently difficult or novel situations	Anxiolytics

Adapted from: Ryan JM, Kidder SW, Daiello LA, Tariot PN. (2002) Psychopharmacologic interventions in nursing homes: what do we know and where should we go? *Psychiatric Services*. 53(11):1407-13.

regimen or mood stabilizers. The critical issue is that these are testable hypotheses and should be treated as such. Target behaviors and baseline frequencies should be identified prior to treatment and an adequate but time-limited trial prescribed. It should be clearly decided what the endpoint is and if the desired goal is not attained, the medication should be discontinued and an alternative conceptual scheme considered.

### **Role of Behavioral and Environmental Interventions**

It is important to point out that individuals with cognitive impairment of all kinds, including individuals with TBI have a heightened sensitivity not only to medications, but to the environment in which they live. This is related to several factors.

*Stimulus Boundedness* As mentioned earlier one of the characteristics of damage to frontal-subcortical circuits with attendant problems in executive function and social comportment is that individuals have great difficulty with components of attention including complex, selective, and sustained attention. This results in difficulty with prioritization of incoming stimuli and the gating out of stimuli that would ordinarily be deemed of secondary importance. At its essence this may be a problem assigning or decoding proper salience to the constant influx of environmental cues and stimuli. In any event the result is that the individual becomes hostage for at least very sensitive to, events in their immediate environment.

*Fondness for Routine* Individuals with cognitive deficits are often quite sensitive to changes in routine or

schedule. This may relate to the afore-mentioned deficits in executive function in which problems with problem solving and mental flexibility can be quite apparent. Over time individuals (injured or non-injured) develop routines that tend to maximize predictability and efficient function, and minimize stress. Changes in these routines call for mental flexibility and problem solving skills to maintain environmental homeostasis. Individuals challenged in these domains will often respond with anxiety, irritability, or even catastrophic reactions to these changes in routine. This tendency can be apparent in response to both changes in people in their environment or changes in time or schedule. The latter may relate to basic impairments in both sense of time and memory, resulting in ongoing anxiety and perseverative requests for information or re-assurance with respect to upcoming events or activities. Family/caregivers and staff often function as cognitive prosthetic devices that the individual relies upon to supply ongoing memory for events, maintenance of schedule, and overall sense of time. Being deprived of these human prosthetic devices is a frightening experience and can result in appearance of some very challenging behaviors.

*Predictability of Response* Injured and non-injured individuals alike base much of minute to minute and long-term decisions and actions on predictions of the response a given action will produce. Increasing the probability of favorable responses and decreasing the likelihood of undesirable responses are powerful forces in shaping behavior. However certain executive deficits such as inferential reasoning, self-monitoring, self-correction, and episodic memory are critical to the successful application of these experiences to shaping behavior. In this context predictability of response becomes even more critical to



maximize contextual learning and generalize these lessons to other novel settings. Individuals existing in an environment in which the same behaviors elicit different responses from different people at different times can become confused, anxious, and agitated.

Thus it is critical to carefully consider these factors when performing a neuropsychiatric assessment. To ignore the environment and factors that may be provoking challenging behaviors will greatly reduce the efficacy of any prescribed medication even if it is the proper medication. On the other hand, without the properly prescribed medication, even massive efforts at applied behavioral analysis and environmental manipulation may be in vain. The therapeutic issue should not be: "Do we prescribe a drug, or write a behavioral plan?" Rather the question is better framed as "Which medicine prescribed in the context of what changes in environment and strategies for shaping behavior has the best potential for success?"

## CONCLUSIONS

Attention to the diagnosis and management of the neurobehavioral sequelae of TBI can serve a critical role in advancing the rehabilitative process. It requires a knowledge and understanding of the profile of regional structural and neurochemical injury associated with the typical TBI and how that profile predicts the common neurobehavioral sequelae. Careful assessment requires an accurate description of the individual's functional and neurobehavioral status prior to the injury, and how that has changed subsequent to the injury. It is helpful to be aware of the problems in diagnosis in individuals who have a fluctuating behavioral baseline, who may have significant cognitive deficits, or in whom the usual connection between internal feeling state and external behaviors may be uncoupled. Treatment should follow from a clearly articulated diagnostic scheme and should be time-limited and re-evaluated in the presence of poor or incomplete response.

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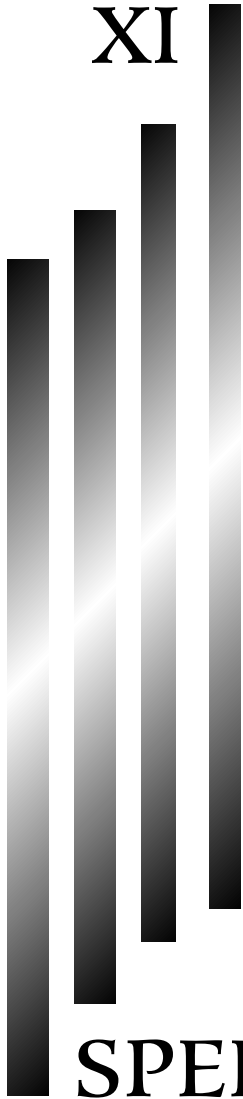
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XI



**SPEECH, LANGUAGE, AND  
SWALLOWING PROBLEMS**



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# 46

## Assessment and Treatment of Speech and Language Disorders in TBI

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### COMMUNICATION DISORDERS FOLLOWING TBI: AN INTRODUCTION

Traumatic brain injury (TBI) is the result of impact-induced biomechanical forces upon neural tissue, including compression, acceleration–deceleration and rotational acceleration (1, 2). Associated neurological injuries may be focal, multifocal, or diffuse, involving direct trauma, as well as tension-related tearing of tissue and/or shearing as a consequence of rotational force (1). In relation to communication skills, the potentially wide-ranging and heterogeneous nature of TBI accommodates an infinite range of prospective motor speech and language disturbances, through effects on the cortical, subcortical, bulbar and/or cerebellar systems.

Of particular note, the integrity of an individual's communication skills subsequent to TBI is often a critical factor in determining post-injury quality of life (3). Indeed, it has been recognized that speech and language deficits resulting from TBI may impose substantial social (4, 5) and vocational (6) ramifications. In the case of adults, the speech and language corollary of TBI is accountable for social segregation, academic failure, and/or vocational demotion following injury (2). In the case of children, TBI has been documented to cause immediate communication deficits, as well as a potential predisposition to speech and/or language

impediments evident during the formative years, whereby infants fail to meet milestones as they proceed along an anticipated motor-cognitive developmental continuum (2). Until recently, the remediation of communication problems associated with TBI has been considered subordinate to the management of related medical conditions (7). In light of the potentially adverse psychosocial impact that a loss of an ability to communicate may impose upon individuals with TBI, however, it must be emphasized that effective speech-language rehabilitation can no longer be viewed as an ancillary treatment objective.

Dysarthria represents a frequently documented symptom of TBI. It reportedly constitutes more than one-third of the communication deficits within this population (8). Furthermore, a diverse range of dysarthric subtypes has been observed in individuals subsequent to TBI (8). Within these subtypes, reported levels of motor speech dysfunction have been documented to vary from mild articulatory imprecision to nonfunctional speech (9). In contrast, apraxia of speech constitutes a rarely documented motor speech anomaly associated with TBI (10–12); however, it has been reported to manifest in tandem with dysarthria and aphasic symptoms in some cases (11). We are precluded in this chapter from discussing this further due to the limited amount of research available pertaining to apraxia in TBI, and the frequently

encountered diagnostic conundrum faced by clinicians with respect to delineating between the symptoms of simultaneous motor programming and muscular control deficits.

Current knowledge about the impact of TBI upon linguistic function is somewhat secondary to that about influences upon motor speech control. This discrepancy may be attributed to the fact that individuals with TBI have been historically reported to perform within normal limits on assessments of general language function (13), largely resulting in the exclusion of this population from supplemental linguistic analysis. Utilizing appropriately sensitive measures of higher-order, in addition to primary language function, deficits at the cognitive–linguistic interface, have been recently identified in TBI subjects (14). Similarly to motor speech sequelae, the nature of linguistic impairments resulting from head injury have been reported as variable (13). Incidence rates with respect to language dysfunction, however, have been documented to be as high as 100% in some research (15), highlighting TBI patients as a clinically viable population for language screening and intervention.

Mild TBI (mTBI) has received attention in the popular media as a public health concern (16, 17). Despite the fact that the majority of neurobehavioral alterations that result from mTBI have been documented to resolve within months of the related trauma, recent evidence suggests that premorbid levels of functioning may never be returned to after an injury (16). Of note, speech and language constitute neurobehavioral domains implicated within this population (18). Clearly, TBI encompassing the full spectrum of severity levels has the capacity to have an impact upon communication proficiency. It is the aim of this chapter, therefore, to describe the speech and language deficits that may manifest in individuals with TBI, as well as to provide a summary of applied assessment and treatment techniques that may be readily integrated within contemporary rehabilitation programs.

## ASSESSMENT AND TREATMENT OF MOTOR SPEECH DISORDERS IN TBI

The variable nature of the neuropathology resulting from TBI predicts the potential involvement of isolated or manifold motor speech subsystems. Consequently, emergent motor speech profiles in TBI subjects may include articulatory, velopharyngeal, laryngeal and/or respiratory deficiencies. A characteristic common to the dysarthria associated with TBI, however, is its intractable nature (8). Of note, it has been documented that although frequently presenting in tandem with language impairments at onset, the dysarthria of TBI endures long after initial linguistic deficits have resolved (3, 19, 20). Recent outcome studies, however, have indicated that the dysarthria of TBI

may respond effectively to a range of treatment techniques, documented to facilitate improvements in clinical speech features, functional communication skills, and physiological substrates (21–28). The following section outlines the nature of motor speech impairments associated with TBI, suitable assessment techniques and relevant treatment approaches.

### The Dysarthria of TBI: Neuroanatomical Classification and Clinical Features

As mentioned previously, the precise nature of the dysarthria that manifests as a consequence of TBI is governed by the location and scope of neural damage endured (8). The inherently diffuse nature of TBI, however, typically accommodates potential disruption at exponential loci along the neural axis, implicating upper as well as lower motor neuron systems. Indeed, classifications of spastic (29), hyperkinetic/hypokinetic (30, 31), flaccid (32, 33), ataxic (27, 34, 35) and mixed (29, 36) dysarthria have been reported within the TBI literature (37); however, spastic (37) and more recently mixed (i.e., spastic-ataxic) (36) subtypes have been highlighted as the most prevalent motor speech disturbances in this population. This motor speech profile is consistent with diffuse bilateral hemispheric damage following head injury (37), potentially implicating terminal loci of the neural fulcrum, such as the frontal lobes (38–40) and cerebellum, as the neuropathological substrates of the dysarthria of TBI.

#### Spastic Dysarthria

Spastic dysarthria, resulting from upper motor neuron damage implicating cortical motor areas and/ or associated descending motor tracts (41), reportedly manifests as a result of wide-ranging disturbance across the motor speech subsystems, characterized by hypertonicity of the muscles and reduced range, speed and strength of muscle excursion (42). Perceptually, this physiological symptom complex is typically characterized by strained-strangled vocal quality, as well as reduced alternate motion and speech rates (42).

#### Hyperkinetic and Hypokinetic Dysarthria

Although less common than spastic dysarthria, upper motor neuron damage as a consequence of TBI has also been reported to result in hypokinetic or hyperkinetic dysarthric subtypes (37). Neuropathologically defined within extrapyramidal nuclei such as the basal ganglia and divisions of the brain stem, hyperkinetic motor behavior denotes aberrantly excessive movement and hypokinesia, diminished and decelerated movement (1). Clinically, hyperkinetic dysarthria is characterized by disturbances in the rhythm and rate of oromotor movements as a consequence of involuntary motor actions, and

variability in muscle tone (43, 44). Perceptually, this profile is most often distinguished by prosodic deviations including impairments in pitch and volume control, stress, rate, phrase as well as inter-word and phoneme duration, but may also include additional aberrant speech features such as sudden respiratory inhalations and exhalations, vocal arrest, strained-strangled vocalization, articulatory imprecision and hypernasality (43–46).

In contrast, the clinical characteristics of hypokinetic dysarthria embody oromotor deviations associated with rigidity, diminished range as well as force of movement, and variations in movement velocity (47, 48). Perceptually, these neuromuscular disturbances commonly manifest as monopitch, monoloudness, reduced stress, festinatory speech (i.e., short rushes), hoarse and/ or breathy vocal quality, articulatory imprecision, phoneme repetition, low pitch, overall increased but variable speech rate and diminished volume control (47–49).

### **Flaccid Dysarthria**

In keeping with the inherently heterogeneous nature of neurological damage associated with TBI, motor speech disturbances consistent with lower motor neuron lesions have also been observed within this population. Resulting from damage to the motor cranial and/ or spinal nerves, flaccid dysarthria is characterized by muscular weakness, absent or reduced reflexes, muscle atrophy and fasciculations (1). Clinically, the motor speech deficits associated with this neurological profile may vary, dependent upon the specific cranial nerves implicated (50, 51). A common assemblage of deviant speech features, however, has been observed in flaccid dysarthric populations including breathiness, audible inspiration, hypernasality, nasal emission, reduced phrase length, consonant imprecision, vocal harshness, monopitch and monoloudness (45). Of particular note, the resonatory and phonatory deficiencies frequently seen in flaccid dysarthria have been described as largely unique to this dysarthric subtype (50).

### **Ataxic Dysarthria**

Extending further along the neural axis, cerebellar damage has also been reported as a possible outcome of TBI (8). Ataxic dysarthria constitutes the resultant motor speech deficit and is typically characterized by articulatory and prosodic insufficiencies (52). Perceptually, these insufficiencies translate as articulatory imprecision (encompassing both consonants and vowels), articulatory breakdowns, excess and equal stress, prolongation of phonemes and inter-word intervals, diminished speech rate, monopitch, monoloudness and harsh vocal quality (53). This motor speech profile has been reported to specifically represent the neuromuscular effects of reduced tone and coordination, effecting slow and inaccurate motor behaviors

relevant to the force, range, timing and direction of speech musculature movement (52, 54).

### **Mixed Dysarthria**

The heterogeneous and often pervasive nature of TBI, respecting lesion location, has also been associated with the clinical presentation of mixed dysarthria, concomitantly encompassing the motor speech deviations of several dysarthric subtypes (1, 37, 55). Notably, a recent body of research identified mixed dysarthria as the most prevalent form of motor speech impairment in cohort of TBI subjects, including spastic-ataxic, spastic-hypokinetic, spastic-flaccid, flaccid-ataxic and spastic-flaccid-ataxic subtypes (8, 36). Of further interest, within this group individuals classified with mixed dysarthric subtypes demonstrated the most qualitatively severe motor speech disturbances, suggesting that more diffuse brain damage may correlate with more severe speech disturbances.

### **Dysarthria Acquired During Childhood**

The aforementioned neuroanatomical classification of dysarthric subtypes and associated clinical features largely relate to motor speech anomalies acquired in adulthood or at neurodevelopmentally stable life stages. Historically, this taxonomy has been adopted as a frame of reference to classify dysarthria resulting from TBI in childhood, however, not without recognised limitations (56). It has been eloquently acknowledged that the pathophysiological mechanisms underlying childhood TBI may be disparate to those which take hold within the adult brain, particularly when considered within the context of developmental hierarchies and neuroplasticity capabilities (56). Indeed, TBI in childhood has been documented to recover more rapidly than that endured in adulthood, as a consequence of distinctive neuroplasticity mechanisms (57). Furthermore, children have been reported to predominantly endure brain injuries as a result of low speed motor vehicle accidents or falls, in opposition to adolescents and adults, commonly involved in high-speed collisions (57). These factors suggest that the mechanisms of child versus adult TBI may be incongruent, with greater rotational acceleration effects and consequently more diffuse brain damage expected in adult populations (56, 57).

Until recently, the perceptual and physiological features of dysarthria resulting from TBI in childhood have been relatively unexplored (58). Contemporary research, however, has revealed similar dysarthric profiles in children as compared to adults following TBI, with respect to the presentation of a variable array of disturbances in prosodic, resonatory, phonatory and articulatory aspects of speech production (56). Despite these clinical parallels, future research investigating the nature of interactions

between developmental and acquired factors is considered critical to the better elucidation of mechanisms underpinning dysarthrias contracted in childhood (59). In particular, resultant motor speech impairments may represent a maturation-sensitive consequence of head injury, within the context of developmental neurological systems. As such, longitudinal monitoring of motor speech abilities in children with TBI is considered pivotal to the prompt identification and remediation of speech deficits that may potentially manifest at any point during the course of motor development.

### The Dysarthria of TBI: Perceptual, Acoustic and Physiological Evaluation

Conventionally, perceptual speech analysis has provided the main stay of dysarthria assessment (56). Despite offering qualitative insights into the audible deviations apparent in dysarthric speech, these methods proffer little with respect to empirically identifying the neuromuscular locus or neurophysiological basis of the presenting deficits. Recently, advancements in technology have catalysed the development of more objective motor speech assessment tools, affording the compilation of quantitative acoustic and physiological profiles by way of state of the art instrumentation. Notwithstanding the value of the data generated via instrumental assessments, speech is by its very nature an audible entity, its “normalcy” considered by some to be most efficiently judged by the human ear. To this

end, perceptual and instrumental techniques combined have been recommended as the most effective means of evaluating motor speech dysfunction (56), taking into consideration relevant pathophysiological substrates as well as deviant perceptual features impacting upon functional communication proficiency. The proceeding summary of assessment methods utilized in the evaluation of dysarthria is largely applicable to both adult and paediatric populations. Recommendations have been made, however, with respect to the screening of developmental articulatory/ phonological processes, and/ or accommodating literacy related limitations in children.

### Perceptual Assessment

Comprehensive perceptual evaluations of motor speech function have been described as those which evaluate the 5 major elements of speech production, including: respiration, phonation, resonance, articulation and prosody (56). The perceptual motor speech assessment battery utilized in our research laboratory adheres to this recommendation, providing qualitative judgements pertaining to deviant speech dimensions (i.e., speech feature analysis (60); Fisher–Logemann Test of Articulation Competence (61)), speech intelligibility (i.e., Assessment of Intelligibility of Dysarthric Speech (ASSIDS) (55)) and subsystem dysfunction (i.e., Frenchay Dysarthria Assessment (FDA)(62)). For a more detailed summary of specific assessments applicable to TBI, refer to Table 46-1.

**TABLE 46-1**

#### *Comprehensive Perceptual Motor Speech Assessment Battery Applicable to TBI*

- Assessment of Intelligibility of Dysarthric Speech (55)
  - standardized assessment of severity of dysarthric speech
  - incorporates measure of speech intelligibility at both single word and sentential levels, overall speech rate, rate of intelligible speech and a ratio of communication efficiency
- Frenchay Dysarthria Assessment (62)
  - standardized assessment of neuromuscular systems associated with motor speech production, including: reflexive, respiratory, articulatory, resonatory and phonatory mechanisms
  - provides composite profile relative to status of motor speech subsystem functioning
- Speech feature analysis (60)
  - following reading aloud of a standard citation such as “The Grandfather Passage” (45) or in the case of children who may not be able to read, an oral picture description task, speech samples are analysed and rated according to the presence and severity of 33 possible deviant speech dimensions
  - relevant dimensions encompass five domains of speech production, namely: prosody (i.e., pitch, loudness, phrasing, rate, stress); respiration (i.e., breath support for speech); resonance (i.e., nasality); phonation (i.e, vocal quality); and articulation (i.e., consonant precision, length of phonemes, precision of vowels)
  - also provides an overall rating of speech intelligibility
- Fisher-Logemann Test of Articulation Competence (61)
  - *relevant to childhood TBI*, this assessment generates an articulatory profile which may be further analysed relating to the nature of deviant speech productions within the context of developmental articulatory and phonological errors

### Instrumental Assessment

The instrumental evaluation of dysarthria encompasses both acoustic and physiological assessment techniques. Acoustic assessment is specifically dedicated to the evaluation of voice, providing measures of frequency, amplitude, perturbation and signal noise, as well as temporally constrained aspects of phonation (e.g., maximum phonation time and voice onset time) (63) and is certainly applicable to TBI populations. A number of acoustic analysis systems are available commercially, including the Computerised Speech Lab® (CSL) (Kay Elemetrics Corp.), VisiPitch® (Kay Elemetrics Corp.), CSpeech®, the Canadian Speech Research Environment® (CSRE), MacSpeech Lab II®, and Dr. Speech Science for Windows® (Tiger Electronics) (64, 65). The CSL and VisiPitch, however, represent the most commonly employed acoustic analysis programs, rated as user friendly via the provision of real-time visual displays of acoustic parameters and the facility to store and analyse data (63).

Physiological assessments represent a corpus of instrumentation dedicated to the evaluation of the neuromuscular control mechanisms underlying speech. Available physiological apparatus not only evaluate phonatory aspects of speech production, but also extend to the assessment of articulation, resonance and respiration, including devices such as the Laryngograph, Electromagnetic articulograph, Nasometer and RespiTrace. Refer to Table 46-2 for summary of physiological instrumentation that may be utilized in the assessment of individuals with TBI.

### Physiological Measures of Laryngeal Function

In relation to the physiological assessment of laryngeal function, electroglottography (EGG) and measures of laryngeal aerodynamics represent two of the most commonly applied physiological tools in the clinical assessment of voice (63). EGG provides a means of representing vocal fold vibratory patterns (66, 67) and aerodynamic measures generate information pertaining to the interaction of various phonatory parameters. Waveforms generated via electroglottographic methods (e.g., Fourcin® Laryngograph) correspond to the opening and closing phases of the glottal cycle, and the velocity at which the vocal folds adduct (65). Measures of laryngeal aerodynamics such as the Aerophone II®, provide indices relating to the interplay of various laryngeal mechanisms in the production of voice, such as subglottal pressure, phonatory air flow, sound pressure level and laryngeal airway resistance (63). In addition to the parameters mentioned above, the Aerophone II® is also capable of measuring vocal fold adduction-abduction rates (68). Of note, high variability rates in performance have been reported in studies of aerodynamic laryngeal function (63). In order to counteract these variability effects, it has been recommended that the average of at least 5 repetitive samples, should be established as a representative illustration of laryngeal function on such measures (69). Within the context of TBI, however, fatigue effects as a result of effortful or repetitive physiological assessment tasks must also be considered in the interpretation of such data (63).

### Physiological Measures of Respiratory Function

Assessments of laryngeal function routinely co-occur with an evaluation of respiratory mechanisms underlying speech production (63). Physiological measures of speech breathing may be divided into 2 broad categories: 1) spirometric (i.e., direct measures of lung volume and capacity) and 2) kinematic (i.e., indirect measures of lung function by way of monitoring chest wall activity during breathing cycles and speech production tasks). Dry spirometers provide a means of measuring a range of respiratory parameters, including: vital capacity, inspiratory capacity, expiratory and inspiratory reserve volumes, forced expiratory volume, respiration rate, tidal volume and volume/ flow relationships. Furthermore, each of the parameters obtained may be compared to predicted age, height and sex-based values by way of formulae weighted for age and/ or height (70, 71).

Kinematic measures of speech breathing provide independent yet simultaneous recordings of alterations in rib cage and abdomen volumes during speech and non-speech tasks. A range of kinematic instrumentation has been applied to the study of speech breathing in neurologically impaired populations (68), including magnetometers,

**TABLE 46-2**  
*Physiological Instrumentation Utilized in the Assessment of Dysarthria Following TBI*

Laryngeal function	<input type="checkbox"/> electroglottographic assessment (Laryngograph®) <input type="checkbox"/> aerodynamic assessment (Aerophone II®)
Respiratory function	<input type="checkbox"/> spirometric assessment <input type="checkbox"/> kinematic assessment (RespiTrace®) <input type="checkbox"/> aerodynamic assessment (AerophoneII ®)
Articulatory function	<input type="checkbox"/> lip and tongue pressure transduction systems <input type="checkbox"/> electropalatography (EPG) <input type="checkbox"/> electromagnetic articulography (EMA)
Velopharyngeal function	<input type="checkbox"/> Nasometer® (Kay Elemetrics) <input type="checkbox"/> accelerometric assessment

strain-gauge belt pneumographs and inductance plethysmography (72–74). RespiTrace®, an inductance plethysmographic measure of respiratory function, is the instrument of choice in our research laboratory. This instrument monitors changes in chest wall circumference via electrical inductance. Wires contained within elasticised straps placed around the chest and abdomen register dimensional alterations during specified tasks. A visual display signal is generated for analysis purposes and may also function as a biofeedback tool during therapy.

### **Physiological Measures of Articulatory Function**

In relation to the evaluation of articulatory function, pressure transduction systems are commonly employed to measure lip and tongue strength, endurance, velocity of movement, and fine force control. Within our research laboratory a miniaturised pressure transducer (Entran Flatline®, Entran Devices Inc., Model EPL 20001–10) with factory calibration, mounted upon an aluminium strip, is used to measure interlabial pressures during speech and nonspeech tasks, resembling that initially described by (75). Similarly a rubber-bulb pressure transduction system is utilized to evaluate tongue function, in line with that described by (76–78).

Electropalatography (EPG) and electromagnetic articulography (EMA) represent measures of dynamic articulatory function. More specifically, EPG provides a means of evaluating the positioning and timing of tongue to hard palate contacts during speech, via a thin acrylic palate studied with miniature sensory electrodes, fitted within a subject's oral cavity. Contact patterns during speech are subsequently acquired and stored in an external processing unit for analysis. By way of transmitter and receiver coil systems generating electromagnetic fields, the Electromagnetic Articulograph® (EMA) AG-100 (Carstens Medizintechnik, Germany) provides a two-dimensional representation of articulatory movements (79). More specifically, the EMA has the capacity to generate kinematic articulatory parameters, including trajectory, velocity, duration and acceleration, via the tracking of displacement relative to receiver coils positioned on the midline of the tongue, upper and lower lips, velum and mandible.

### **Physiological Measures of Velopharyngeal Function**

Measures of nasal airflow, air pressure, vibration and oro-nasal acoustic output offer non-invasive, clinically viable methods of assessing velopharyngeal competence (80). Nasal accelerometry and measures of oro-nasal acoustic output ratios represent the assessments of velopharyngeal function utilized routinely within our research laboratory. Nasal accelerometry involves the placement of miniature,

vibration sensitive accelerometers upon the lateral nasal cartilage and thyroid lamina, which detect nasal and laryngeal vibrations during speech. The magnitudes of vibration detected are then used to calculate a ratio of nasal to laryngeal vibration, providing an index of nasality, the Horri Oral Nasal Coupling (HONC) index (81, 82). High HONC indices are considered representative of velopharyngeal incompetence.

The Nasometer® (Kay Elemetrics) offers a measure of nasality via the generation of oro-nasal acoustic output ratios (83–85). Two directional microphones separated by a sound-separating plate are positioned anterior to the nose and mouth which record acoustic output signals. Accompanying software calculates nasalance scores which effectively represent nasal to oral acoustic output ratios during various speech tasks. High scores are considered representative of velopharyngeal dysfunction.

### **The Dysarthria of TBI: Treatment Approaches**

The treatment of the dysarthria of TBI in both child and adult populations has been described as a convoluted and protracted process, necessitating consideration of individual deficits within the context of functional communication requirements (86). The International Classification of Functioning, Disability, and Health (ICF) offers a widely-accepted framework for intervention relative to domains of health (87), which encompass communication skills. Within this model, the treatment of dysarthria is viewed from a three-tiered perspective, including: (1) integrity of body function and structure; (2) associated activity limitations and participation restrictions; (3) contextual factors facilitating functional improvements/ reduction in disability.

The inherently heterogeneous nature of the dysarthria associated with TBI respecting lesion site and severity, has largely precluded the reporting of group outcome studies relative to individual treatment techniques (88). By and large, research pertaining to treatment effects has been conducted via single case study designs, reporting the impact of a range of behavioral, instrumental and prosthetic approaches (22–26, 89–97).

### **Behavioral Approach**

The behavioral approach to the rehabilitation of dysarthric speech involves the teaching of compensatory strategies via traditional methods, which encompass the presentation of therapeutic stimuli and the establishment of response contingencies (98). The principle goal of this approach is to facilitate functional gains in speech intelligibility (99) via neuromuscular therapeutic techniques (100). These therapies include active exercises (e.g., strength training), stretching (e.g., to increase or decrease

tone), passive exercises (e.g., massage to relax musculature), and the use of physical modalities such as heat (to reduce pain), cold (to reduce spasticity) and electrical stimulation (to elicit voluntary contractions) (100). Historically, traditional/ behavioral techniques have provided the mainstay of dysarthria therapy, given their economic viability and wide-ranging environmental utility (101). Although failing to constitute an unabridged stockpile of behavioral dysarthria therapy techniques, Table 46-3 represents a number of commonly utilized traditional approaches in the remediation of phonatory, respiratory, resonatory, articulatory and prosodic deficits.

### Instrumental Approach

The instrumental therapeutic approach incorporates techniques which offer direct physiological or biofeedback pertaining to motor speech subsystem function during therapy tasks. Biofeedback tools provide a means of re-establishing motor control patterns by way of unconventional or adjunct sensory channels (113). Sensory channels may incorporate auditory, visual or tactile modalities, however, visual feedback signals have been documented as the most effective in the remediation of dysarthria (114–116). Table 46-4 highlights a range of biofeedback techniques currently utilized in the treatment of

respiratory, phonatory, resonatory, articulatory and prosodic disorders.

### Prosthetic/ Surgical Approach

Prosthetic and/ or surgical interventions, which effectively modify the physical configuration of specific motor speech subsystems (98), are commonly employed in the remediation of severe dysarthria (101). Table 46-5 summarises a range of prosthetic/ surgical techniques utilized the treatment of motor speech impairments, usually employed subsequent to an ineffective trial of more traditional therapeutic approaches.

### CASE REPORTS: CLINICAL MANAGEMENT OF DYSARTHRIA FOLLOWING TBI

The ability to apply the previously highlighted principles of dysarthria assessment and treatment to the management of a clinical caseload represents a requisite skill for any clinician. Within the context of the framework for intervention outlined in the ICF (87), the following vignettes constitute proposed clinical management plans relevant to the treatment of dysarthria following TBI, in a 26 year old adult and a 14 year old child.

**TABLE 46-3**  
*Behavioral Therapeutic Approaches in the Treatment of Dysarthria Following TBI*

TARGETED MOTOR SPEECH SUBSYSTEM	METHOD
• Phonation	<ul style="list-style-type: none"> <li>□ <i>Hyperadduction reduction techniques</i>: aim to alleviate excessive vocal fold adduction by way of tension reduction techniques such as <i>chewing</i> (102), <i>yawn-sigh</i> and <i>gentle voice onset</i> methods (103)</li> <li>□ <i>Hypoadduction reduction techniques</i>: aim to achieve effective vocal fold adduction and effective phonation in dysphonic patients via the application of <i>push/pull</i> (104), <i>hard glottal attack</i> (105), and <i>increased phonatory effort</i> (106) methods</li> </ul>
• Respiration	<ul style="list-style-type: none"> <li>□ <i>Manipulating posture</i> to maximize respiratory control (107) via the provision of visual, tactile and/ or auditory cues</li> <li>□ <i>Inspiratory checking</i> (108) technique aims to increase breath support and enhance respiratory control during exhalation via drills which encourage the regulation of air flow and volume during vocalization</li> </ul>
• Resonance	<ul style="list-style-type: none"> <li>□ Exercises aimed at increasing range of movement and strength of velum including <i>blowing, gagging and sucking</i> (101), as well as palatal awareness via <i>visual feedback</i> (101), <i>palatal massage</i> (109) and <i>icing/ brushing</i> (110) techniques</li> </ul>
• Articulation	<ul style="list-style-type: none"> <li>□ Aim to normalise function of the articulators (i.e., lips, tongue and jaw) via the <i>modification of muscle tone</i> (e.g., hypertonia versus hypotonia), <i>maximising muscle strength</i> (i.e., isotonic and isometric oromotor exercises (109, 111)) and <i>articulation/ speech drills</i> of increasing complexity (98)</li> </ul>
• Prosody	<ul style="list-style-type: none"> <li>□ Methods aimed at remediating stress patterning (e.g., <i>contrastive stress drills</i> (109)), intonation (e.g., <i>altering respiratory capacity and patterning</i> (112)) and rate (e.g., <i>intersystemic reorganization</i> (109) involving therapist directed pacing of speech)</li> </ul>



**TABLE 46-4**  
***Instrumental Therapeutic Approaches in the Treatment of Dysarthria Following TBI***

TARGETED MOTOR SPEECH SUBSYSTEM	METHOD
• Phonation	□ Use of apparatus with the facility to display vocal parameters such as pitch, intensity and duration during speech output (e.g., Vocalite (117), Visipitch (112), Visispeech (118), Speech Viewer (91), storage oscilloscope (119))
• Respiration	□ <i>U-tube manometer</i> : requires patient to maintain specific water level over designated period of time via controlled exhalation (109) □ <i>Kinematic instrumentation</i> (e.g., <i>Respirace</i> ®): provides visual representation of chest wall movements during speech tasks. Feedback shown to be effective in increasing lung volumes, increasing abdominal contributions to breathing as well as enhancing co-ordination of speech breathing (95, 120)
• Resonance	□ <i>Endoscopy</i> and <i>flexible fibre nasopharyngoscopy</i> provides direct visual feedback pertaining to velar and posterior pharyngeal wall excursion during speech (121, 122) □ <i>Velograph</i> provides real time representation of velar movement via an oscilloscope (123) □ <i>Nasometer</i> ® provides bar graphs and/ or real time visual displays of nasalance during speech (101)
• Articulation	□ <i>Electromyography (EMG)</i> represents a biofeedback tool with applications for altering labial and lingual muscle tone and strength (26, 92, 124–126) □ <i>Electropalatography (EPG)</i> may be utilized as a biofeedback device to alter lingual postures during speech (127, 128)
• Prosody	□ <i>Speech Viewer</i> (129) provides both visual and auditory feedback pertaining to fundamental frequency and vocal intensity. Documented as successful device in improving pitch, intonation and rate of speech (130) □ Modification of speech rate during reading via <i>PACER computerised rhythmic cueing</i> (131) □ <i>Delayed Auditory Feedback (DAF)</i> documented as useful biofeedback device in reducing rate, increasing vocal intensity and enhancing overall speech intelligibility (132–134)

**TABLE 46-5**  
***Prosthetic and/or Surgical Approaches in the Treatment of Dysarthria Following TBI***

TARGETED MOTOR SPEECH SUBSYSTEM	METHOD
• Phonation	□ <i>Voice amplifiers</i> : electronic device aimed at increasing voice volume (112, 135) □ <i>Botox injections</i> (136), <i>laryngeal nerve resections</i> (137) in the treatment of hyperadduction □ <i>Reinnervation of paralysed vocal folds</i> (138), <i>collagen/ Teflon implants</i> (139, 140) and <i>arytenoid adduction</i> (141) in the treatment of hypoadduction
• Respiration	□ <i>Abdominal muscle girdling</i> by way of elasticised bandages (109). Enhances expiratory control during speech by facilitating recoil of the abdominal musculature. □ Postural enhancement by use of <i>overhead slings</i> (109). Provides surface upon which individuals may bear down to establish expiratory force for speech.
• Resonance	□ <i>Palatal lift prosthesis</i> aims to achieve palatopharyngeal closure (142, 143)
• Articulation	□ <i>Bite block</i> to increase jaw stability and maximize function of other articulators and/ or <i>palatal augmentation prosthesis</i> which aims to facilitate tongue/ palatal contacts required for articulation otherwise compromised by reduced range of movement or elevation of tongue (143, 144)
• Prosody	□ <i>Pacing</i> (145)/ <i>alphabet board</i> (146) encourages speech rate reduction

### **Case 1 (Adult): Moderate Spastic-Ataxic Dysarthria (86).**

*Case History:* Jacob is a 26-year-old male who sustained a TBI as the result of a motor vehicle accident. On admission to hospital a Glasgow Coma of score of 5 was reported, indicative of severe head injury. MRI investigations revealed bilateral subcortical hemorrhages and multiple contusions. At the time of his accident, Jacob was married and working as a practicing accountant. His family and employer were reportedly committed to his rehabilitation and return to the work force.

*Motor Speech Profile: Moderate Spastic-ataxic Dysarthria:* Perceptual assessment results revealed: reduced speech intelligibility, consonant imprecision, reduced breath support for speech, hypernasality, strained-strangled vocal quality, reduced pitch and loudness control, reduced speech rate and impaired stress patterning. Physiological assessment revealed wide-ranging motor speech subsystem dysfunction, incorporating: reduced respiratory support for speech, hyperfunctional laryngeal activity, velopharyngeal insufficiency and reduced range and speed of labial and lingual movement.

*Clinical Management Plan:* A multisystem approach was adopted in the rehabilitation of Jacob's speech, involving a combination of behavioral and instrumental treatment techniques. Consistent with the ICF, his presenting motor speech deficit was considered in relation to structural and functional impairments, imposed activity limitations and participation restrictions as well as manipulable contextual factors. Refer to Table 46-6 for the proposed rehabilitation schedule.

### **Case 2 (Child): Moderate Spastic Dysarthria (147)**

*Case History:* Max is a 14-year-old male who sustained a TBI following a pedestrian/ motor vehicle accident. On admission to hospital a Glasgow Coma of score of 5 was reported, indicative of severe head injury. Computed tomographic (CT) scan revealed soft tissue hematoma over right temporal and left zygomatic regions as well as an area of high attenuation in left lentiform nucleus and additional foci scattered over peripheral grey/ white region anteriorly and superiorly. No significant mass effect was observed. At the time of his accident, Max was a high-achieving year 9 high-school student with a range of extracurricular interests, including: debating, football and tennis.

*Motor Speech Profile: Moderate Spastic Dysarthria:* Subsequent to TBI, Max endured a 5-month period of mutism. Perceptual assessment of speech function following this period revealed: severely reduced range and

speed of lingual movement; moderately reduced range and speed of labial movement, consonant imprecision, strained-strangled vocal quality, hypernasality, reduced breath support for speech, slow speech rate, monopitch and moderately reduced speech intelligibility. Physiological assessment also revealed wide-ranging motor speech subsystem dysfunction, incorporating: reduced lung volumes and capacities as well as reduced abdominal excursion during speech, laryngeal hyperfunction, velopharyngeal insufficiency and reduced labial and lingual strength and endurance.

*Clinical Management Plan:* A multisystem approach was again adopted in the rehabilitation of Max's speech, involving a combination of behavioral and instrumental treatment techniques. Consistent with the ICF, his presenting motor speech deficit was considered in relation to structural and functional impairments, imposed activity limitations and participation restrictions as well as manipulable contextual factors. Refer to Table 46-7 for the proposed rehabilitation schedule. Furthermore, longitudinal monitoring of Max's speech and language abilities was considered pivotal in maximising educational and subsequently vocational potential, as he continued to mature from adolescence into adulthood.

## **ASSESSMENT AND TREATMENT OF LANGUAGE DISORDERS IN TBI**

Detailed investigations of linguistic integrity subsequent to TBI have been afforded limited consideration within the scientific literature thus far (13). The forerunning explanation for this lack of inquiry may rest with the observation that TBI subjects tend to perform within normal limits on tests of general language function, routinely incorporated within linguistic screening batteries. Despite this admission, however, recent evidence indicates that TBI proffers distinct ramifications for cognitive-linguistic substrates underpinning complex language processes, the rudiments of which fail to be adequately evaluated via standard aphasia tests.

Consequently, the proceeding sections of this Chapter highlight the nature of language impairments following TBI, appropriately sensitive assessments of linguistic function for use within adult and pediatric populations, as well as relevant treatment strategies.

### **Linguistic Deficits and TBI: Taxonomy and Neural Substrates**

Despite being reported to largely perform within the range of normal on assessments of general language function, individuals with TBI frequently demonstrate deficiencies in relation to functional communication

**TABLE 46-6**  
**Multisystem Approach to the Rehabilitation of Moderate Spastic Dysarthria Following TBI in an Adult: Jacob**

TREATMENT GOAL	METHOD
<ul style="list-style-type: none"> <li>• Reducing impairment in body structure and function. Remediate physiological dysfunction within motor speech subsystems.               <ul style="list-style-type: none"> <li>○ Enhance coordination of chest wall movements during speech</li> <li>○ Remediate hyperadduction of vocal folds</li> <li>○ Increase velopharyngeal competence</li> <li>○ Increase strength and range of labial and lingual movements</li> </ul> </li> <li>• Reducing activity limitations and participation restrictions. Enhance speech intelligibility.               <ul style="list-style-type: none"> <li>○ Modify stress and intonation patterns</li> <li>○ Increase speech rate</li> <li>○ Enhance articulatory precision</li> </ul> </li> <li>• Maximising communicative success across a range of communication environments               <ul style="list-style-type: none"> <li>○ Increasing communication partner awareness of conversational topics and contextual cues</li> <li>○ Repairing communication breakdowns</li> <li>○ Capitalizing upon situational and environmental recompense to maximize effectiveness of communication</li> </ul> </li> <li>• Manipulating contextual factors. Enhancing opportunities for participation across social and vocational contexts</li> <li>• Providing information to family/ friends/ workmates pertaining to nature of communicative disability and strategies to enhance communicative effectiveness within social and vocational environments</li> </ul>	<ul style="list-style-type: none"> <li>➤ Kinematic instrumentation to offer visual feedback of chest wall movement</li> <li>➤ Chewing/ yawn-sigh, gentle voice onset techniques</li> <li>➤ Use of Nasometer® to provide visual feedback of nasalance during speech</li> <li>➤ Isometric and isotonic lip and tongue exercises</li> <li>➤ Contrastive stress and intonation drills</li> <li>➤ PACER technique</li> <li>➤ Articulation drills</li> <li>➤ Practice routinely identification of contextual cues and establishment of topic of conversation</li> <li>➤ Clarify if communication partner has comprehended intended message and provide strategies for communication partners to request clarification</li> <li>➤ Limit communicative interactions when fatigued and maximize interaction when energy levels are at their peak; avoid noisy environments</li> <li>➤ Provide resources outlining: the cause and nature of presenting communication deficit; strategies to maximize communicative success with unfamiliar communication partners (e.g., sitting in front partner, requesting clarification in the event of misunderstood message)</li> <li>➤ Provide assistance in communicatively taxing situations (e.g., board meetings; face to face client contact)</li> </ul>
<p>*Note: References pertaining to individual treatment techniques may be located in Tables 46-3, 46-4, and 46-5.</p>	

skills (148–153). Furthermore, where TBI individuals do present deficits in primary language function such as naming, verbal association, reading and/ or auditory comprehension (150, 154, 155), error profiles generally fail to meet the criteria for classification within traditional Bostonian taxonomies (149). On the basis of these characteristics, a coherent conceptualisation of the nature of linguistic deficits associated with TBI has been hindered thus far.

Most recently, however, measures of high-level linguistic functioning including probes of metalinguistic ability, lexical-semantic manipulation and language

integration, have been recognised as sensitive indices of cognitive-linguistic breakdown in TBI populations (14). Tasks involving: the interpretation of ambiguous sentences, making inferential judgements, semantically constrained sentence generation, interpretation of metaphorical expressions and humour, formation of semantic associations, identification of semantic absurdities, synonym and antonym generation, definition and multiple definition formulation have been specifically implicated. These tasks are considered to be complex in nature, potentially necessitating the interplay of cognitive (e.g., attention, memory, executive

TABLE 46-7

**Multisystem Approach to the Rehabilitation of Moderate Spastic Dysarthria Following TBI in a Child: Max**

TREATMENT GOAL	METHOD
<ul style="list-style-type: none"> <li>• Reducing impairment in body structure and function. Remediate physiological dysfunction within motor speech subsystems               <ul style="list-style-type: none"> <li>○ Increase strength, range and speed of labial and lingual movements</li> <li>○ Increase breath support for speech</li> <li>○ Remediate hyperadduction of vocal folds</li> <li>○ Enhance velopharyngeal closure</li> </ul> </li> <li>• Reducing activity limitations and participation restrictions. Enhance speech intelligibility.               <ul style="list-style-type: none"> <li>○ Enhance articulatory precision</li> <li>○ Increase speech rate and enhance pitch variation</li> </ul> </li> <li>• Maximising communicative success across a range of communication environments               <ul style="list-style-type: none"> <li>○ Increasing communication partner awareness of conversational topics</li> <li>○ Repairing communication breakdowns</li> <li>○ Capitalizing upon situational and environmental recompense to maximize effectiveness of communication</li> </ul> </li> <li>• Manipulating contextual factors. Enhancing opportunities for participation across social and educational contexts               <ul style="list-style-type: none"> <li>➤ Providing information to family/ friends/ teachers pertaining to nature of communicative disability and strategies to enhance communicative effectiveness within social and educational environments</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>➤ Isometric and isotonic lip and tongue exercises; timed alternate motion exercises</li> <li>➤ Inspiratory checking technique</li> <li>➤ Chewing/ yawn-sigh, gentle voice onset techniques</li> <li>➤ Use of accelerometer to provide visual biofeedback during nasal/ non-nasal contrasts</li> <li>➤ Articulation drills</li> <li>➤ Speech Viewer® to provide auditory and visual feedback re: rate and pitch parameters during speech tasks</li> <li>➤ Max to consistently orient communication partner to topic of conversation and to maximize use of contextual cues (e.g., environmental props)</li> <li>➤ Clarify if communication partner has comprehended intended message and offer revisions when needed</li> <li>➤ Write message if not understood</li> <li>➤ Avoid noisy environments; utilize friends and family to assist in communicative interactions with unfamiliar partners or in unfamiliar environments</li> <li>➤ Provide resources outlining: the cause and nature of presenting communication deficit; strategies to maximize communicative success with unfamiliar communication partners (e.g., ask for clarification if Max's speech is unable to be understood; ask him to write messages in the event of communication breakdown; move to a quiet environment; affirm comprehension of conversational topic with close friends</li> <li>➤ Oral assessment items/ debating (e.g., english orations may be written by Max and tape recorded by family member/ friend for class presentation)</li> <li>➤ Utilization of flash cards for scoring when umpiring game of tennis</li> </ul>

\*Note: references pertaining to individual treatment techniques may be located in Tables 46-3, 46-4, and 46-5.

function) and linguistic processes (156). It is this interface that appears to be most susceptible to the effects of TBI, as opposed to more general language processes.

Overall communicative competence has also been postulated to necessitate the interplay of cognitive-linguistic processes which facilitate access to and manipulation of the semantic system within contextually defined environments

(13), extending well beyond the domain of operational or primary level language (157). Indeed, some research has highlighted frontal lobe dysfunction as the primary substrate underlying the language impairments associated with TBI, on the basis of diminished neuropsychological test results pertaining to frontal lobe integrity in tandem with reduced language performance (158). In support of this

postulate, closed head injury has been hypothesised to yield its greatest impact upon the prefrontal cortex, by virtue of skull configuration (159). It is plausible, therefore, that the interplay of frontal lobe-dependent cognitive domains such as attention, memory, executive function etc. with linguistic processes may be subsequently impaired as a result of TBI.

Linguistic deviations interwoven within a tapestry of cognitive deficits represents a commonly accepted view of the language symptom complex associated with TBI (13, 149, 155, 160). The precise nature of cognitive-linguistic interactions within this population, respecting a hierarchy of domain-specific influences upon language function, however, remains largely unknown (13). Recently, TBI performance profiles on tasks of lexical-semantic manipulation (e.g., TWT-R) have been strongly correlated with the cognitive variables of memory and attention (14), potentially earmarking these variables as integral to the mediation of certain linguistic operations.

In a similar manner to motor speech correlates, the linguistic sequelae of TBI have been documented as extremely variable from case to case (14), perhaps best attributed to variations in neuropathology across subjects. Despite this heterogeneity, however, several studies have identified subgroups within TBI populations respecting language performance (161–163). Global cognitive-linguistic impairment to near normal levels of functioning have been reported, with and without concomitant combinations of attentional, memory and/ or visuospatial deficits (162, 163). These profiles suggest that certain aspects of language are indeed influenced and perhaps directed by cognition, evidenced by distinct yet variable levels of discernable association subsequent to brain injury.

Thus far, the focus of the discussion pertaining to linguistic impairments associated with TBI has been directed at adult populations. Brain injury within childhood, or developmentally formative life stages with respect to cognitive skill acquisition, however, must be afforded special consideration. In a similar manner to adult language disturbances as a result of TBI, children with head injuries have been documented to present a form of “subclinical aphasia” (164), or rather, symptom complexes which fail to comply with the primary characteristics of traditional aphasic syndromes. For example, previous studies have specifically reported impairments on task of verbal fluency (165–168), confrontation naming (167, 169–171), verbal repetition (170, 171) and written expression (164, 172). Although not representative of frank aphasic deficits, it has been hypothesized that these atypical profiles may reflect the impact of TBI upon language processes in developmental ascendancy at the time of insult (164).

In line with adult research, post-TBI language profiles in children suggest impairment of a high-level linguistic nature, particularly when the aforementioned deficits are

considered within the context of well-documented neuropsychological deviations, including: disturbances of memory, attention, visuospatial ability and executive function (173–175). Indeed, following this line of investigation, reduced scores on sentence generation, as well as ambiguity and figurative language interpretation tasks have been identified in children with TBI (176).

Despite the many clinical parallels that may be drawn between language syndromes associated with adult and pediatric TBI, children potentially present deficits against a developmental backdrop, providing distinctive implications for assessment and treatment. Of most note, TBI in children has been documented to disproportionately disturb the acquisition of new language skills as compared to the recovery of already established abilities (177), and the younger a child is at the time of injury, the more profound the effect on language function (172, 178). Furthermore, latent behavioral deficits have also been reported to manifest in children with TBI (179, 180), posing definite ramifications for educational and vocational potential. These caveats indicate that assessment and treatment plans must be carefully mapped out in the treatment of paediatric head injury, as much as to enhance communicative competence as to maximize the quality of present and future life opportunities.

### Linguistic Deficits and TBI: Assessment

In general, individuals with TBI have been reported to demonstrate distinctive deficits on high-level language tasks which entail: (i) the application of metalinguistic competence; (ii) linguistic integration/ reasoning; (iii) divergent language production; (iv) lexical-semantic manipulation (i.e., judgement, organization, retrieval) (13). Subsequently, assessment batteries utilized in the evaluation of TBI individuals should incorporate such measures. Relevant assessments as they relate to adult and pediatric populations have been listed in Tables 46-8 and 46-9, respectively. Acknowledging the potential for varying levels of deficit severity in TBI populations, assessments of primary language function may also be required to delineate impairments in some individuals. As per high-level language evaluation, refer to Tables 46-8 and 46-9 for recommended assessments of general language function as they apply to adult and pediatric cases.

It has also been acknowledged that the conversational speech of TBI subjects is frequently characterized by verbosity, tangentiality and idiosyncratic phraseology (152). Parameters such as these are inadequately assessed via standard aphasia batteries. Consequently, contemporary research has begun to focus upon the assessment of more dynamic versus static linguistic functions in TBI, including discourse, or language in its most naturalistic form (181). A comprehensive summary of discourse and its analysis as it relates to TBI is beyond the scope of this Chapter. Suffice

**TABLE 46-8**  
**Recommended Linguistic Assessment Battery:**  
**Adult TBI (14, 181)**

General Language Function
<input type="checkbox"/> Western Aphasia Battery (WAB) (182)
<input type="checkbox"/> Boston Diagnostic Aphasia Examination (BDAE) (183)
<input type="checkbox"/> Boston Naming Test (BNT) (184)
<input type="checkbox"/> Neurosensory Centre Comprehensive Examination for Aphasia (NCCEA) (185)
<input type="checkbox"/> The Revised Token Test (186)
High-level Linguistic Function
<input type="checkbox"/> Test of Language Competence-Expanded (TLC-E) (187)
<input type="checkbox"/> The Word Test-Revised (TWT-R) (188)
<input type="checkbox"/> The Test of Word Knowledge (TOWK) (189)
<input type="checkbox"/> Wiig-Semel Test of Linguistic Concepts (WSTLC) (190)
<input type="checkbox"/> The Right Hemisphere Language Battery (RHLB) (191)
Discourse
<input type="checkbox"/> Story Retell: The Businessman and the Tramp (181)

**TABLE 46-9**  
**Recommended Linguistic Assessment Battery:**  
**Childhood TBI (192)**

General Language Function
<input type="checkbox"/> Receptive-Expressive Emergent Language Test, Second Edition (REEL 2) (INFANTS) (193)
<input type="checkbox"/> Preschool Language Scale-3 (PLS-3) (Birth-6 years) (194)
<input type="checkbox"/> Clinical Evaluation of Language Fundamentals, Preschool (CELF-P) (3-6 years) (195)
<input type="checkbox"/> Clinical Evaluation of Language Fundamentals, Third Edition (CELF 3) (6-16 years) (196)
<input type="checkbox"/> Peabody Picture Vocabulary Test, Third Edition (PPVT-III) (197)
<input type="checkbox"/> Hundred Pictures Naming Test (HPNT) (198)
<input type="checkbox"/> Boston Naming Test (BNT) (184)
High-level Linguistic Function
<input type="checkbox"/> Test of Language Competence, Expanded (TLC-E)
<input type="checkbox"/> Test of Word Knowledge (TOWK) (189)
<input type="checkbox"/> Test of Problem Solving, Elementary (TOPS-Elementary) (199)
<input type="checkbox"/> Test of Problem Solving, Adolescent (TOPS-Adolescent) (200)
Phonological Awareness
<input type="checkbox"/> Queensland University Inventory of Literacy (QUIL) (201)
<input type="checkbox"/> Test of Phonological Awareness (TOPA) (202)
Discourse
<input type="checkbox"/> School Age Oral Language Assessment (SAOLA) (203)

to report that discourse analysis of non-interactive (e.g., narrative, procedural, expository) and interactive language samples has provided valuable insights into the nature of the functional linguistic impairments associated with TBI (181). Discourse analysis may involve the evaluation of syntactic, thematic and/ or information variables (181) as well as the more pragmatic aspects of communication, or the application of social rules (204), including turn-taking, maintenance of topic, comprehension of verbal and nonverbal cues etc. (205-207). Possible methods of language sample acquisition for discourse analysis have been listed in Tables 46-8 and 46-9, however, for a detailed discussion of analysis techniques, the reader is referred to (181, 208, 209).

### Linguistic Deficits and TBI: Treatment Approaches

The rehabilitation of cognitive disorders resulting from TBI, including language deficits, essentially involves three general approaches, including: restorative, compensatory and/ or behavioral techniques (210-213). Restorative techniques involve the undertaking of repetitive tasks targeting specific neural processes, with the aim of restoring function. Compensatory techniques involve the development of strategies and/ or competencies which overcome prevailing deficits via the acquisition of functional skills (213). Behavioral techniques engage behavior modification strategies in the development of targeted skills (210). In most cases, these strategies are used in combination, the restoration of behaviors and behavioral compensations representing the products of intervention.

#### Behavioral/ Restorative Approach

Specifically targeting impairments, traditional/ restorative approaches to language rehabilitation involve the repetitive undertaking of structured linguistic tasks, the nature of which are determined following a psycholinguistic evaluation of cognitive-linguistic integrity (214, 215). Refer to Table 46-10 for some examples of restorative therapy tasks.

#### Compensatory Approach

The compensatory approach to linguistic rehabilitation entails the development of self-initiated strategies to overcome particular communicative deficits, by way of physical props (e.g., written notes), external cues (e.g., requests for repetition of information) or internalized or self-cueing (208, 216). The success of compensatory approaches has been reported to rely upon the user's ability to apply them automatically (208). Consequently, compensatory strategies utilized naturally by a particular individual will be automatized more quickly than those strategies that are foreign or unfamiliar. For examples of compensatory strategies, please refer to Table 46-11.

**TABLE 46-10**  
*Restorative Therapeutic Strategies in the Treatment of Linguistic Deficits Following TBI (208)*

Deficit	Therapy Task
• Lexical-semantic Processing	<ul style="list-style-type: none"> <li>➤ Generating synonyms and antonyms</li> <li>➤ Word-definition matching</li> <li>➤ Convergent and divergent naming</li> </ul>
• Comprehension of complex linguistic information	<ul style="list-style-type: none"> <li>➤ Interpreting abstract expressions</li> <li>➤ Proverb/metaphor explanation</li> <li>➤ Discriminating between fact and opinion</li> <li>➤ Following instructions of increasing length and complexity</li> </ul>
• Organization of verbal expression	<ul style="list-style-type: none"> <li>➤ Sequencing tasks</li> <li>➤ Story retelling</li> <li>➤ Narrative production using specified schemas</li> </ul>

### TREATMENT APPROACHES: PEDIATRIC CONSIDERATIONS

By and large, the same treatment approaches may be applied to the rehabilitation of linguistic deficits as a consequence of TBI endured in childhood. In the case of pediatric populations, however, therapeutic hierarchies must not only focus on the remediation of skills already established at the time of injury, but must also take into account the future acquisition of developmental language processes. Of particular note, the impact of TBI on cognitive-linguistic functioning may not always manifest immediately following insult in children (208). Associated language deficits may only become apparent when the child fails to successfully acquire specific language processes relevant to a developmental continuum. As a result, children with acquired brain injuries should be monitored longitudinally in order to permit the prompt identification and remediation of potential cognitive-linguistic anomalies, with a view to promoting a sound educational and vocational platform.

### CASE REPORTS: CLINICAL MANAGEMENT OF LINGUISTIC IMPAIRMENTS FOLLOWING TBI

The following vignettes present clinical management plans relative to the rehabilitation of linguistic deficits following TBI in a 23-year-old adult and a 9-year-old child.

**TABLE 46-11**  
*Compensatory Therapeutic Strategies in the Treatment of Linguistic Deficits Following TBI (208)*

DEFICIT	STRATEGY
• Verbosity with good insight into maladaptive behavior	➤ Frequent clarification with communication partner that they are following conversation
• Verbosity with poor insight into maladaptive behavior	➤ Obtain assistance of external communication partner regarding relevance of verbal output
• Word retrieval problems with natural tendency to circumlocute	➤ Utilize circumlocution as a means of facilitating word retrieval
• Ineffective functional communication	➤ Identify where communication breakdowns occur (i.e., in what environments), formulate communication strategies for use in those environments and develop skills by way of functional therapy tasks (e.g., role playing)

### Case 1: Linguistic Impairment Following TBI in Adulthood

*Case History:* Kylie was a 23-year-old kindergarten teacher and part-time student at the time she sustained a TBI as the result of a motor vehicle accident. She was unconscious at the accident scene. However, no Glasgow Coma Score was recorded. Neuroimaging investigations failed to identify any focal neurological damage. At the commencement of her rehabilitation program, returning to work as a kindergarten teacher was her consummate goal.

#### *Language Profile:*

- Primary-level language largely intact with evidence of word retrieval deficits
- Natural inclination to utilize circumlocution as a means of facilitating word retrieval
- High-level linguistic deficits evident. Reduced performance on tasks of lexical semantic manipulation (e.g., forming semantic associations, defining words with multiple meanings, constructing semantically constrained sentences).
- Narrative discourse analysis revealed a proliferation of verbal disruptions, general verbosity

- Conversational discourse presented a similar profile, marked by intricate details in the presentation of information whereby the original theme of the message was often times forgotten. Kylie was insightful pertaining to her verbose communication style, frequently acknowledging her tendency to ramble.
- Often demonstrated overfamiliarity and inappropriate communicative behaviors with unfamiliar communication partners, with little insight pertaining to these character traits.

Based on the above information and within the context of the framework for intervention promoted by the ICF, a functional cognitive-linguistic communication plan for Kylie's rehabilitation was devised (208), 3 months subsequent to injury. This plan specifically targeted levels of impairment, activity limitation and participation restriction, and has been illustrated in Table 46-12.

### Case 2: Linguistic Impairment Following TBI in Childhood

*Case History:* Sally was a 9-year-old primary school student who sustained a TBI as the result of a fall from a horse. No loss of consciousness was observed at the time of injury but she was not responsive to commands. A Glasgow Coma Score of 7 was recorded at hospital admission. CT scan failed to reveal any focal neurological damage, however, a left occipital skull fracture was indicated.

Two days after hospital admission, Sally's condition deteriorated to a state of deep coma, requiring ventilation for a period of 1 week. Subsequent CT scan revealed right cerebral oedema, compressed ventricles and midline shift. Limited verbal output was observed post-injury with the gradual return of simplified yet socially appropriate language, 4 weeks following insult. Speech/ language evaluation at this time revealed:

#### Language Profile:

- Primary-level language largely intact with evidence of deficiencies in aspects of spoken language production, such as confrontation naming
- Conversational discourse was marked by circumlocutory behaviors, frequent repetition of utterances, difficulty interpreting humour and comprehending complex instructions
- Delayed responses to test items evident
- Overall, high-level linguistic impairment impacting upon communicative competence was diagnosed. General profile was characterized by reduced verbal fluency and word retrieval skills in the presence of impaired performance on tasks requiring comprehension of complex concepts and instructions.

**TABLE 46-12**  
*Cognitive-Linguistic Rehabilitation Plan Following Adult TBI: Kylie*

GOAL	METHOD
<ul style="list-style-type: none"> <li>• Providing effective instructions to children the preschool setting</li> </ul>	<ul style="list-style-type: none"> <li>➢ Maximize verbal retrieval and planning by way of: (i) utilising circumlocution as a means of facilitating word retrieval; (ii) plan one sentence explanations increasing hierarchically to more complex structures; (iii) structured lexical-semantic tasks (e.g., naming to definition; convergent naming; divergent naming etc)</li> <li>➢ Provide opportunities for role playing and rehearsal</li> </ul>
<ul style="list-style-type: none"> <li>• Reduce verbosity in conversation</li> </ul>	<ul style="list-style-type: none"> <li>➢ Discuss content categories such as relevant, irrelevant and embellishment</li> <li>➢ Discuss narrative structure</li> <li>➢ Identify presence and absence of content within conversations</li> <li>➢ Establish self-initiated cues to reduce verbosity</li> <li>➢ Provide opportunities for role playing, video feedback, group therapy</li> </ul>
<ul style="list-style-type: none"> <li>• Develop appropriate conversational style with unfamiliar communication partners</li> </ul>	<ul style="list-style-type: none"> <li>➢ Discuss various communication contexts, appropriate and inappropriate communication styles</li> <li>➢ Provide opportunities for role-playing and video feedback to enhance self-monitoring skills</li> </ul>

Based on the above information and within the context of the framework for intervention promoted by the ICF, a functional cognitive-linguistic communication plan for Sally's rehabilitation was devised (217). Refer to Table 46-13 for specific treatment schedule. Sally received 6 months of intensive speech pathology intervention with regular monitoring of progress including a formal language review at 12 months post-injury. At this point, the majority of linguistic deficits had resolved with the exception of subtle word finding difficulties in conversation. Ongoing speech pathology intervention involved monitoring of language recovery, as well as the implementation of compensatory strategies, tailored to changeable educational and social needs over the course of Sally's academic life.



**TABLE 46-13**  
***Cognitive-Linguistic Rehabilitation Plan***  
***Following Childhood TBI: Sally (217)***

GOAL	METHOD
<ul style="list-style-type: none"> <li>• Reduce word finding difficulty</li> </ul>	<ul style="list-style-type: none"> <li>➤ Convergent naming</li> <li>➤ Identify salient features relative to specified items</li> <li>➤ Utilize salient features strategy to facilitate word retrieval in conjunction with communication partner</li> <li>➤ Story retell/ story construction</li> </ul>
<ul style="list-style-type: none"> <li>• Enhance comprehension of complex material</li> </ul>	<ul style="list-style-type: none"> <li>➤ Following instructions of increasing length and linguistic complexity</li> <li>➤ Interpreting ambiguous sentences and figurative language; explaining jokes</li> <li>➤ Provide opportunities to request repetition of information when information not understood (e.g., role play in classroom environment)</li> <li>➤ Provide classroom strategies: request teachers to write complex instructions down when not understood; provide written summary of each class; engage in tutorials at end of lesson to ensure Sally has understood main concepts; regular contact with parents and monitoring of academic progress</li> </ul>

### **MILD TBI: MORE THAN MEETS THE EYE?**

To date, TBI research has largely focused upon the effects of moderate to severe level trauma, typically incorporating cases that have demonstrated extended periods of lost consciousness (18). It has been long acknowledged, however, that an absence of frank neurological disturbance subsequent to head injury does not guarantee an unmarred recovery (218). Indeed, physical, cognitive and affective disturbances constitute frequently documented sequelae associated with concussion or mTBI (219).

The majority of mTBI behavioral research to date has been neuropsychologically-based, lacking in-depth linguistic analyses (220). Reduced processing speed, concentration, attention and memory (219) have been identified as common cognitive deficits in mTBI patients.

Respecting language, deficits in verbal fluency, story recall/ verbal memory and anomaly detection (221–224) have also been reported, suggesting that higher-level linguistic processes may be implicated following mTBI. Indeed, a comprehensive language evaluation recently conducted within our laboratory was in support of this hypothesis. Deficits in lexical access, complex lexical-semantic manipulation at single word and sentential levels, as well as the organization and monitoring of responses were highlighted in a single mTBI case, nearly 2 years post-injury (225).

Potential high-level language implications in mTBI are supported by a neuroanatomical rationale. In an absence of frank neurological disturbance, dynamic imaging studies relating to cerebral perfusion and metabolism, have revealed frontal and temporal lobe abnormalities in mTBI cases (226–229). In terms of localisation theory, these findings have evident implications for language function. The mTBI language profile identified within our laboratory closely paralleled that of frontal lobe disconnection populations previously studied (230–235). This finding supports the notion that mTBI mechanisms may also preferentially implicate frontal lobe systems involved in the recruitment and directed interplay of the frontal lobes with other language areas, perhaps via neuronal fall out processes (236).

With respect to speech, it has been generally accepted that motor speech disturbances commonly accompany severe TBI (237). Within the domain of mTBI, however, speech deficits have also been documented (172, 238–240). The precise nature of these disturbances remains unexplored, with detailed perceptual and physiological investigations of motor speech function sorely lacking.

Acceleration-deceleration trauma without explicit neurological deficit has been recognized in simian research to evoke diffuse degenerative changes in axonal functioning (241). Shear strain (238) induced axonal injury has been hypothesised to result in the degeneration of synaptic terminals as well as disturbed neuronal input (242–244). Evidently, the extent of axonal damage subsequent to mTBI may involve the complete neural axis, extending from the cortical regions mentioned previously, to terminal aborizations within the brain stem (241). These neurophysiological alterations resulting as a consequence of mTBI, provide a platform for explaining the physical, cognitive and affective sequelae frequently associated with this syndrome. The potentially wide-ranging neuropathological profile of mTBI also offers possible ramifications for speech and language function, including manifestations of subclinical oromuscular and cognitive-linguistic alterations that may be undetected by standard assessments of fine motor control and cognitive abilities.

If we consider that the demands placed upon mTBI patients are greater at any given time after injury than that

of patients with severe brain trauma (245), the challenge lies ahead for researchers and clinicians to evaluate and apply appropriately sensitive methods of assessment to this population, in an effort to better delineate the nature of associated communication deficits. Special attention must be afforded to mTBI endured in childhood, considering that subtle symptoms may be easily camouflaged by inherent variabilities in maturational rates, particularly in regard to neuropsychological factors (18). Furthermore, ascertaining whether or not the communicative sequelae of mTBI demonstrate responsivity to traditional treatment techniques is yet to be determined.

The neuropsychological literature currently provides the mainstay of data pertaining to the assessment and treatment of mTBI cohorts (220). Contemporary studies have recently reported efficacious outcomes subsequent to a process-specific approach to the remediation of working attention/ memory deficits (246), and the implementation of compensatory strategies for functional impairments of memory, attention, reasoning and additional components of executive function (247). The development and application of cognitive communication rehabilitation techniques relative to this population, however, is much needed. To this end, it is anticipated that Speech-Language Pathologists may have a potentially valuable role to play in the future educational and/ or vocational rehabilitation of individuals with mTBI, as the precise nature of the motor/ cognitive sequelae associated with this syndrome continue to be unraveled.

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# 47

## Evaluation and Treatment of Swallowing Problems After TBI

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**T**raumatic brain injury in children or adults can affect swallowing in a variety of ways (1–4). It is important for the clinician to investigate the history of the patient’s original injury and acute care for that injury in order to understand the type(s) of swallowing disorders that may be present. The neural damage resulting from traumatic brain injury and the incident causing the injury can vary tremendously from patient to patient. There is the direct neural damage at the site of trauma, the contrecoup injury or the opposite side of the brain trauma as the brain bounces in the brain case, and there is the twisting or torquing of the brainstem during the injury. Thus, there is rarely a direct relationship between the location of the trauma and the nature of the swallow disorders. However, the clinician should learn the locus of the direct injury and results of any other testing of neural function to identify other areas of damage (5).

In addition to the neural damage, there is potential structural damage during the injury that could affect swallowing. For example, if the patient’s neck is broken as their head is injured, they may exhibit problems in swallow related to cervical spine injury (6). If the patient flies from a motor vehicle and lands on a foreign body such as a stick or piece of metal, there may be penetrating wounds into the neck that affect swallowing. Thus, the exact nature of the patient’s damage at the scene of

the accident is quite important. Another factor in identifying swallowing disorders in the patient who has suffered a traumatic brain injury, is to define any emergency medical care that could affect swallowing (7). This would include an emergency tracheostomy, which might be placed higher in the neck than normal and damage laryngeal function. If intubation to establish an airway is done traumatically, it can cause dislocation of one or both arytenoid cartilages or other damage to the larynx, particularly the true vocal folds. Understanding the nature of the patient’s injuries and the medical care they received is important in accurately assessing dysphagia in the head-injured patient. The key to successful recovery/rehabilitation of dysphagia after brain injury is to define the exact structural or physiologic abnormalities in the swallow and to design the therapy program to address these disorders.

*Swallowing Disorders Seen in Brain Injury* A broad range of swallowing disorders is seen in patients after brain injury, probably because of the wide range of damage that can cause dysphagia in these patients. If the patient exhibits upper motor neuron damage with high muscle tone, there may be difficulty in opening the mouth, controlling the oral tongue and the soft palate. Most commonly, there is a delay in triggering the pharyngeal swallow or even an absent pharyngeal swallow. There may



be reduced motor control of the pharyngeal stage of swallow when it triggers, involving reduced movement of the tongue base to generate pressure to move the food into the pharynx, reduced laryngeal elevation because of scar tissue, tracheostomy, etc., or there may be reduced pharyngeal wall contraction resulting in reduced pressure generation. Dysfunction in the airway protection provided by the larynx does not occur frequently in head-injured individuals nor does a dysfunction at the upper esophageal sphincter at the entrance of the esophagus. However, patients with structural damage can have scar tissue in place that affects either airway closure or opening of the upper esophageal sphincter. Myoclonus may occur in any oral or pharyngeal structure including the oral tongue, tongue base, soft palate, pharyngeal walls, larynx, and completely discoordinate the swallow. It is critical that the speech language pathologist define the exact nature of the patient's swallowing disorder(s) in order to define appropriate therapy/management for the patient's swallowing problem(s).

*Counseling the Patient's Family* In a patient who has suffered a severe brain injury, swallowing is often one of the last things to be evaluated. Sometimes, patients are allowed to eat because they exhibit no symptoms of a swallow disorder such as coughing or choking. Then, later, as recovery progresses, the patient begins to exhibit some signs of dysphagia while swallowing particular types of food. It is important that clinicians talk with the patient's physician and family as soon as possible regarding the possibility of swallowing disorders and the potential need to evaluate swallowing. Families often think that if the patient is not visibly struggling to eat, coughing and choking, their swallowing is fine. If the patient is allowed to eat and then later has an assessment which identifies a significant swallow impairment, families and patients can become very angry, complaining that they were allowed to eat at an earlier stage in recovery sometimes at another institution, but now the clinician is "making them go backwards" and delaying their recovery. Because of this reaction, it's important that clinicians introduce the possibility of a swallow impairment early, even if evaluation isn't possible immediately because of the patient's medical status.

*Evaluation of Dysphagia in Brain Injured Patients: When and How* The evaluation of dysphagia in brain injured patients should begin as they are admitted to the acute care hospital. However, in some situations, the patient receives a severe enough injury that swallowing evaluation is not even considered until the patient has been stabilized and life is no longer threatened. **For some patients this may be days or weeks.** The initial screening assessment may simply indicate that the patient is not ready for a full swallowing assessment. Many patients are

in a coma initially. A small amount of data point to the fact that the longer the coma, the more severe the swallow problems are likely to be (3). When the patient is consistently awake and exhibits some level of alertness, dysphagia assessment should begin at the bedside. Formal swallowing evaluation and therapy have been found to improve dysphagia outcomes in brain injured patients (8)

Bedside assessment usually includes an oral motor assessment, a review of receptive and expressive language and ability to understand direction, history of medications used since the injury, and oral sensory testing to identify any abnormal oral reflexes or postural abnormalities (9). The major purpose of the bedside clinical assessment is to identify oral motor difficulties in the face, lips, tongue, palate, pharynx, and larynx, and to determine whether there is significant risk of a pharyngeal stage swallowing impairment. Pharyngeal stage swallowing impairments cannot be diagnosed at the bedside and require an instrumental assessment in order to define the exact nature of the swallowing problem and its sequelae such as inefficient swallow or aspiration. A review of the patient's medications may identify medications that could negatively affect swallow including tranquilizers, psychotropics, and medications that cause xerostomia (10). Oral sensory assessment examining two point discrimination and light touch sensitivity is important in determining the patient's ability to recognize where food is located in the mouth and whether or not all of the food has been cleared in any swallow attempt. Some brain injured individuals exhibit severely slowed oromotor control such that opening the mouth can take 3 to 5 minutes. In this situation, there is generally significant hypertonicity in facial musculature which requires rotary massage on one cheek while digital pressure downward is applied firmly to the chin and the patient is given repeated directions to try to open their mouth. Even with this assist to heighten sensory awareness, the patient may take 3 to 5 minutes to open their mouth. In such a patient who is also nonverbal, an instrumental swallow assessment must be delayed until they are able to open their mouth in under 30 seconds. The rotary massage and continuous digital pressure to the chin will facilitate faster oral opening as well as an understanding of the patient's neural and structural damage causing the swallowing problem. Family members should be counseled regarding the fact that the patient is not yet ready to have an instrumental swallow assessment but rather needs to build control over their oral mechanism instead. The patient's ability to manage their own saliva and awareness of their saliva is also an important component of the bedside assessment. At the end of a bedside assessment, the clinician should be able to describe the patient's level of alertness, their ability to follow direction, behavior control, their oral motor function and their saliva control as well as understand the patient's neural and structural damage

causing the swallowing problem. Patients should also be assessed for their ability to vocalize and to coordinate respiratory and laryngeal function. If the patient has been given food or is eating, the clinician should observe the patient swallowing to identify any dysphagic symptoms. Unfortunately, the bedside clinical examination cannot define pharyngeal physiology or pharyngeal symptoms of swallow disorders such as aspiration (11).

**Instrumental Assessments** Instrumental assessments may include a radiographic evaluation, fiberoptic endoscopic examination of swallow (FEES) or manometric assessment. Radiographic assessment is the simplest for the patient who has sustained a brain injury since no tube or other instrumentation must be placed into their nose or mouth. During the radiographic assessment, the patient must be able to be positioned into the fluoroscopy equipment so that the head and neck can be viewed in the lateral plane (Figures 47-1 and 47-2). Even this can be difficult for some low level patients. However, in many instances the patient can be moved into the equipment and positioned between the fluoroscopy tube and the table on a cart or gurney, thus requiring no voluntary motor control on their part.

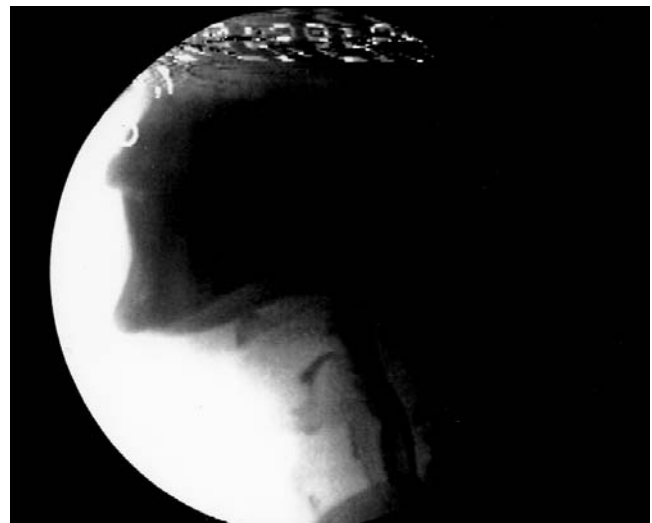
The radiographic study is designed to define the anatomy and the physiology of the oral preparatory, oral and pharyngeal phases of swallow and to identify therapy procedures to improve the swallow if needed. The goal of the test is to find ways for the patient to swallow successfully, not to keep them from eating (12). The patient is given measured volumes of thin liquids, pudding and,

if the patient is capable of chewing, a material requiring mastication, generally a Lorna Doone cookie. Other foods can be given as needed. The patient is presented with measured volumes of thin liquid beginning with a small amount (1 ml) and asked to swallow it. The material is a flavored barium. The patient is given 2 swallows of each bolus volume or food type and the swallow is observed fluoroscopically. In total, the patient should receive 2 swallows each of 1, 3, 5, 10 ml of thin liquids, cup drinking of thin liquids, pudding and masticated material. The bolus volumes of thin liquid are increased sequentially as long as the patient swallows the smaller volume successfully, that is, without aspiration or large amounts of residual food left in the mouth or pharynx. If the patient exhibits a significant swallow impairment which results in aspiration or large amounts of oral or pharyngeal residue, the patient should be given treatment strategies during the x-ray study to improve the swallow and eliminate these sequelae of swallow disorders. Generally, when selected treatment techniques are introduced during the radiographic study, three types of techniques are attempted in the following order: 1) postural change; 2) heightening sensory awareness; and 3) voluntary swallow maneuvers. The specific postural techniques, sensory enhancements and voluntary swallow maneuvers to be introduced with a particular patient will depend upon the nature of their swallowing disorders revealed by the diagnostic portion of the test and the level of their ability to follow direction. The purpose of introducing therapy strategies into the radiographic diagnostic study is to determine which procedures are the most efficacious for the patient and to do so in a way that



**FIGURE 47-1**

Lateral radiographic view of the oral cavity and pharynx after a swallow in a brain injured patient who is also spinal cord injured and is wearing a neck brace. There is significant residue in the mouth and the tongue base is also coated with material



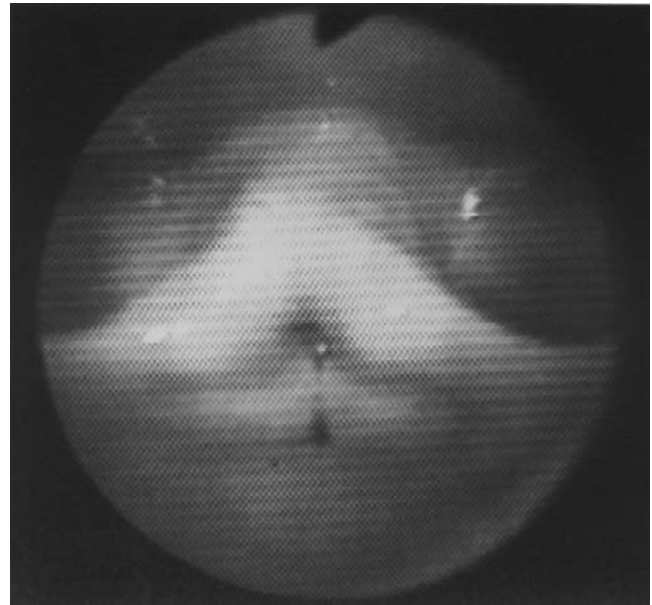
**FIGURE 47-2**

Lateral radiographic view of the oral cavity and pharynx at mid swallow in a patient post brain injury. The airway should be completely closed at this time but there is penetration and aspiration present

documents their effectiveness. If none of these strategies improve the safety or efficiency of the swallow, the clinician can introduce other food consistencies such as nectar- or honey-thickened liquids to determine whether or not the patient can gain a safe and fairly efficient swallow with a diet change. At the end of the radiographic study, the clinician should be able to define the patient's swallow physiology and safety, the best treatment procedures for the patient's swallow disorder(s) and the optimal diet as well as safety of the swallow. The report provided after the study should provide this information in a concise and accurate format.

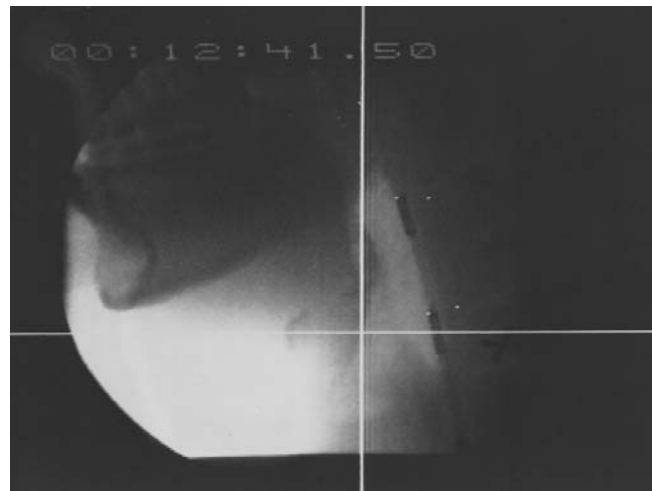
Another instrumental assessment is the fiberoptic endoscopic evaluation of swallowing or FEES which involves the nasal insertion of a fiberoptic tube in order to view the pharynx from above. This procedure does not enable observation of the oral preparatory or oral phases of swallow, nor does it permit assessment of the pharyngeal stage of swallow during the moment of laryngeal elevation, tongue base retraction and upper esophageal sphincter opening (6, 13–14). It does enable observation of the bolus entering the pharynx over the base of tongue, the initial movements of the pharyngeal stage of swallow and any aspiration that may occur as the bolus appears in the pharynx. It also enables viewing of the pharynx after the swallow when any bolus residual may be aspirated. In summary, endoscopy provides a superior view of the pharynx and enables the clinician to observe selected aspects of the oral pharyngeal swallow (see Figure 47-3). Endoscopy has the advantage of involving no radiographic exposure and enabling the clinician to bring the equipment to the patient's bedside (15). The question the clinician must answer is whether or not the endoscopic examination will provide the information needed for management of the patient's swallowing disorder(s).

If the question the clinician needs answered in the swallow assessment is whether or not the pressure generated during swallow is adequate, then manometry may be the appropriate procedure to be used. Many swallowing disorders, including difficulties with the oral tongue, tongue base or pharyngeal wall, lead to reduced pressure generation in the pharynx including reduced movement of the base of tongue, reduced movement of the pharyngeal walls and reduced laryngeal elevation and forward movement. While the radiographic study or the fiberoptic endoscopic study can give a perception of reduced pressure to clear food through the pharynx, actual measurements of pressure can only be made with manometry. Manometry, too, involves placement of a tube transnasally into the pharynx and the top of the cervical esophagus. Generally, this is done under fluoroscopy in order to assure where the pressure sensors in the manometric tube are located (see Figure 47-4) and to determine what structures are touching the manometric tube that may create pressure changes (16).



**FIGURE 47-3**

A superior endoscopic view of the larynx and the pharynx with the false vocal folds closely approximated prior to swallow. The arytenoids and pyriform sinuses are also in view. The upper esophageal sphincter (UES) is located at the top of the image behind the arytenoids and is closed. Opening of the UES is not usually visible during endoscopy as the endoscopic image disappears as the larynx elevates during the first third of the pharyngeal swallow (24, 25)



**FIGURE 47-4**

Lateral radiographic view of the oral cavity and pharynx prior to a swallow with a solid state manometric catheter in place prior to swallow. The manometric catheter is a 3 mm diameter flexible tube containing the solid state pressure sensors represented by the dark elongated rectangles resting on the pharyngeal wall first at the level of the tongue base, and second at the level of the laryngeal entrance

Before scheduling the instrumental assessment, the patient should be screened for their readiness for an instrumental assessment. If the patient is unable to control their behavior or to tolerate leaning against the back of a cart during a radiographic study, then they are not ready for that assessment. Similarly, if the patient is easily upset or will not tolerate a tube placed in their nose, they are not ready for an endoscopic or manometric study in many cases.

Other procedures can be utilized in assessment of dysphagia in brain injured individuals including the use of ultrasound and electromyography. These procedures are not frequently used in the evaluation of swallow function in the brain injured individual because the information that they can provide has limited clinical utility. Ultrasound is an imaging procedure using high frequency sound waves which enables examination of tongue motion in the mouth but does not visualize the pharynx. Since many of the greatest concerns in the patient with dysphagia resulting from a brain injury are pharyngeal concerns, ultrasound will not provide the requisite information. Similarly, electromyography is a procedure that shows electrical activity in muscles being used during swallow but does not enable visualization of oral and oropharyngeal structures or their movement.

In summary, a radiographic study, that is, the modified barium swallow, is the most commonly utilized instrumental assessment to evaluate oropharyngeal swallow abnormalities in the patient who has sustained a brain injury.

## TREATMENT/MANAGEMENT OF DYSPHAGIA IN BRAIN INJURED PATIENTS

The initiation of treatment for dysphagia in the brain injured individual generally depends upon the outcome of the detailed physiologic assessment. In some cases, treatment may begin immediately with exercise programs to facilitate improved swallowing motor control. Or, treatment may involve compensatory strategies in an attempt to direct the flow of food in a more safe or efficient manner. Exercises to reestablish a coordinated swallow may also be appropriate. Each of these will be discussed below.

*Compensatory Treatment* Compensatory strategies to manage swallowing disorders typically involve changes in head or body postures. There are 5 different head and body positions which have known effects on pharyngeal dimensions, the bolus and structural movements during the oropharyngeal swallow: 1) chin down; 2) chin up; 3) head rotated; 4) head tilted; and 5) lying down. Table 47-1 presents these 5 postures and their known effects on the anatomic relationships of structures in the pharynx and

also on the oropharyngeal swallow. Postural techniques are usually attempted first because they are relatively easy for most patients to achieve and can have dramatic effects on the oropharyngeal swallow (17–19). Table 47-1 presents a list of swallow disorders and appropriate postural techniques along with the effects of the posture on swallow function.

*Enhancing Sensory Input* Another set of management procedures involve enhancing sensory input in the patient's oral cavity prior to the attempt to swallow (20–22). Generally, these procedures include thermal tactile stimulation and enhancing the bolus taste, texture, volume, carbonation, or viscosity. The sensory enhancements are appropriate for patients with sensory swallowing disorders which are: 1) a delay in recognition of food in the mouth and a delay in the oral onset of the swallow, and 2) a delay in triggering the pharyngeal swallow. Both of these disorders must be identified in the careful swallow assessment. Sensory treatment procedures such as intensifying or changing bolus taste or presenting carbonation have not been adequately studied. The small amount of available data indicate that such procedures are not effective in patients with impairment in motor control of the oral or pharyngeal stages of swallow.

*Swallow Maneuvers* Swallow maneuvers are voluntary controls applied to selected motor characteristics of the oropharyngeal swallow. There are 4 voluntary swallow maneuvers that have known effects during the motor control of swallow: 1) supraglottic swallow; 2) super-supraglottic swallow; 3) effortful swallow; and 4) the Mendelsohn maneuver. The supraglottic swallow involves a voluntary breath hold lightly before and during the oropharyngeal swallow. This closes the airway at the level of the true vocal folds. The super-supraglottic swallow closes the airway entrance between the arytenoids, base of epiglottis and false vocal folds, thus closing the entrance to the airway. This is done by breath holding with effort. The effortful swallow increases the known pressure exerted during swallow by the oral tongue and tongue base. The patient is instructed to squeeze hard with all of their muscles during swallow. This improves tongue base and oral tongue action and the resultant pressures during swallow. The Mendelsohn maneuver is designed to increase laryngeal elevation and forward movement during the swallow and thereby to increase opening of the upper esophageal sphincter. The sphincter is controlled by hyo-laryngeal movement. The patient is told to swallow normally and as they swallow feel their "voice box" or "Adam's apple" elevate during swallow. When they can feel their larynx elevate, they should grab the larynx with their muscles in the neck and hold the larynx up. The effort of holding the larynx up extends its elevation and increases opening of the upper esophageal

**TABLE 47-1**  
**Postural Techniques Generally Most Appropriate for Each Swallow Disorder and the Physiologic/Anatomic Effect(s) of the Posture on Pharyngeal Dimensions or Bolus Flow**

DISORDER OBSERVED ON FLUOROSCOPY	POSTURE APPLIED	PHYSIOLOGIC/ANATOMIC EFFECT OF POSTURE
Inefficient oral transit (Reduced posterior propulsion of bolus by tongue)	Head back	Utilizes gravity to clear oral cavity
Delay in triggering the pharyngeal swallow (Bolus past ramus of mandible but pharyngeal swallow is not triggered)	Head down	Widens valleculae to prevent bolus entering airway; and narrows airway entrance
Reduced tongue base retraction (Residue in valleculae)	Head down	Pushes tongue base backward toward pharyngeal wall
Unilateral laryngeal dysfunction  (Aspiration during swallow)	Head down  Head turned to damaged side	Places epiglottis in more posterior, protective position  Pushes damaged side toward midline
Reduced laryngeal closure (Aspiration during the swallow)	Head rotated to damaged side and chin down	Increases vocal fold closure by applying extrinsic pressure; narrows laryngeal entrance. Places epiglottis in more protective position
Reduced pharyngeal contraction (Residue spread throughout pharynx)	Lying down on one side	Eliminates gravitational effect on pharyngeal residue
Unilateral pharyngeal paresis (Residue on one side of pharynx)	Head rotated to damaged side	Eliminates damaged side from bolus path Pulls cricoid cartilage away from posterior pharyngeal wall,
Cricopharyngeal dysfunction (Residue in pyriform sinuses)	HEAD ROTATED	reducing resting pressure in cricopharyngeal sphincter

sphincter. These maneuvers can be used during eating or as an exercise. There is another swallow maneuver, the tongue holding maneuver which is an exercise maneuver and cannot be used to eat. During the tongue holding maneuver, the patient holds their tongue tip between their teeth to stabilize it, thereby pulling the tongue base forward and putting extra pull on the muscle which contracts the pharynx at the tongue base level and pulls the tongue base backward, the glossopharyngeal muscle.

All of these maneuvers require the ability to follow direction and thus may not be appropriate for the most severely damaged individuals who have suffered a brain injury. Data on nature of swallow disorders among the brain injured indicate that disorders of airway closure or upper sphincter opening occur relatively infrequently (3). When these disorders do occur among patients with brain injury swallow maneuvers can be very helpful if the patient is able to follow the directions necessary.

**Exercise Programs** Exercise programs can also be very helpful to improve structural range of motion, muscle

strength, and coordination (20). Range of motion exercises are helpful in patients with neurologic or structural damage to the brainstem or to the periphery and are available to the facial muscles, tongue, laryngeal elevation, and laryngeal adduction (20). Strengthening or resistance exercises for the tongue can result in significant improvements (23–24) in tongue function for swallowing. Swallow maneuvers can be used as exercises to improve swallow coordination (25–26). When prescribed, these exercises should be done for short periods (5 minutes, 10 times per day). These exercises can be difficult for brain injury patients with language or cognitive deficits who may not be able to follow directions. Such patients may more successfully use postural changes, sensory enhancements, or diet change.

**Diet Change** Sometimes patients can only swallow safely on a particular viscosity of food, such as thin liquid, nectar thick liquids, honey thick liquids, pudding, etc. Limiting a patient's diet should be the clinician's last choice in management because most patients dislike diet

**TABLE 47-2**  
***Bolus Consistencies and the Swallow Problems for Which They Are Usually Most Appropriate. The Patient Should Be Tested Radiographically with Each Bolus Type to See Which Can Be Most Efficiently and Safely Swallowed***

FOOD CONSISTENCIES	DISORDERS FOR WHICH THESE FOODS ARE MOST APPROPRIATE
Thin liquids	Delayed pharyngeal swallow *Reduced tongue base retraction *Reduced pharyngeal wall contraction *Reduced laryngeal elevation Reduced cricopharyngeal opening *Oral tongue dysfunction
Thickened liquids (nectar and/or honey) Purees and thick foods, including thickened liquids	Delayed pharyngeal swallow Reduced laryngeal closure at the entrance Reduced laryngeal closure throughout the larynx

\*All of these disorders affect generation of pressure to drive the bolus through the oral cavity and/or pharynx. Thinner foods (liquids) require less pressure to swallow.

changes such as thickened liquids. However, there are patients for whom there is no other feasible management and diet change is necessary. Or the patient is recovering and can initially only swallow safely and efficiently on a particular food consistency. Table 47-2 presents food consistencies that are particularly helpful for patients with various oropharyngeal swallow disorders.

*Experimental Treatment Procedures* There are a number of treatment procedures currently being discussed in the area of dysphagia therapy that are experimental in nature because these procedures have no efficacy data to support them. They should be used carefully and only with a very strong rationale. These procedures include neuromuscular electrical stimulation to various points on the neck, deep pharyngeal neuromuscular stimulation (DPNS) and myofascial release. None of these procedures have been identified as effective with any specific swallow impairments or with patients with a specific diagnosis. Therefore, clinicians should approach their application with care, particularly in patients with seizures or muscular hypertension in the head or neck.

### SHORT- AND LONG-TERM FOLLOW UP

It is important that patients who have sustained a brain injury are regularly seen after discharge if therapy has not returned their swallow to a functional status, i.e., no aspiration and only minimal residual food left in the mouth or pharynx after the swallow. There are numerous instances in which patients who have sustained brain injury with subsequent dysphagia have received

swallowing therapy and shown improvement but have ultimately plateaued and have not been able to return to full oral intake. Some of these individuals have been found to have functional swallowing at 3, 6 or 9 months after their original discharge from swallowing treatment. It is clear that we do not know enough about recovery from swallow disorders caused by brain injury. Therefore, it is best to reassess the patient's function at 6 months or a year post discharge from treatment if the patient is left non oral.

### RESEARCH NEEDS

There is a great deal more research needed in the area of brain injury and swallowing disorders. The pattern of recovery of swallow disorders post brain injury has not been clearly defined though it is clear that most patients do recover swallow abilities over the first 3 to 5 months post injury (27). There are some patients, however, who do not achieve functional and safe swallowing or who require much longer rehabilitation (28) and the exact nature of their neural damage or resulting swallowing disorders in comparison to individuals who have achieved faster recovery have not been defined. There have been no clinical trials in the comparative effectiveness of specific strategies for swallowing therapy in patients with brain injury. One reason for this is the wide variety and high variability between brain injured patients with dysphagia. There are numerous patient characteristics that must be controlled but such research is much needed. The relationship between coma duration and severity and the nature of swallowing disorders and recovery time for dysphagia deserve further attention as well.

Factors associated with development of pneumonia in severely brain-injured patients with and without dysphagia have been examined (29). These authors found that a Glasgow Coma Scale Score of less than 5, evidence of swallowing disorders and aspiration and field intubation were risk factors for early pneumonia in the brain-injured patient. However, this issue and others related to recovery of full oral intake in the dysphagic head-injured patient require a great deal more research.

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# 48

## Cognitive-Communication Deficits Following TBI

*Carl A. Coelho*

**L**anguage is best defined within the context of communication. Human communication involves the sharing and exchange of information between people. Language refers to communication through the use of words or other symbols and entails the use of multiple modalities such as: speaking, auditory comprehension, reading, writing, and gesture (1). Language use is frequently displayed through speech. Speech has developed into a highly efficient system for the exchange of even the most complex ideas. However, speech is the end product of a multifaceted cognitive process. For example in a situation in which two people are interacting; the speaker has to organize his thoughts, or communicative intent, decide what he wants to say and put what he wants to say into an appropriate linguistic form. This occurs by selecting the right words and phrases to express the intended meaning, and then placing these words in the correct order specified by the grammatical rules of the language. The next stage involves the formulation of motor commands necessary for programming the speech mechanism (i.e., the neural and muscular activities for activating respiration, phonation, resonance, articulation, and prosody) to produce an acoustic signal that accurately represents the words selected to communicate the speaker's intent. The final step in this process is the

execution of the commands resulting in the production of speech (2).

Brain injuries may disrupt the process of communication at a variety of levels. Speech disorders (e.g., apraxia of speech or the dysarthrias) will not be discussed in the present chapter. The reader is referred to chapter 46 for a thorough discussion of that topic. Rather this chapter will focus on language disorders following traumatic brain injury (TBI).

### **LANGUAGE DISORDERS FROM A SITE OF LESION PERSPECTIVE**

The nature of a brain injury will in large measure determine the characteristics of the subsequent language disorder. For example, strokes are typically associated with focal lesions to either hemisphere or subcortical structures, resulting in fairly predictable deficit patterns. By contrast, TBI may result in focal injury to specific regions of the brain (e.g., coup and contrecoup sites of impact), diffuse axonal injury (i.e., stretching, tearing, shearing of nerve fibers), or a combination of both. This mechanism of injury yields a far less homogenous array of deficits. Language disorders resulting from lesions to the left hemisphere, right hemisphere, subcortical regions, and diffuse damage are reviewed separately below.



### **Focal Left Hemisphere Damage—Aphasia**

McKinley and colleagues (3) have noted that language is disturbed in 75% or more of individuals with TBI. However, the nature of this language disturbance, that is, whether it is aphasic or nonaphasic, is not clear-cut. Aphasia is defined as an acquired impairment of language processes underlying receptive and expressive modalities caused by damage to areas of the brain that are primarily responsible for language function (4). Aphasia is characterized by grammatical disturbances, deficits of word retrieval, auditory comprehension, reading, and writing, in the presence of relatively intact cognitive abilities (e.g., orientation, attention, memory). Lesions associated with aphasia are usually located in the left hemisphere in the region of the posterior frontal lobe, anterior temporal lobe, and/or inferior parietal lobe (i.e., anywhere along the distribution of the left middle cerebral artery). The incidence of aphasia secondary to TBI reported in the literature varies greatly. Reports range from approximately 2% of 750 (5) and 614 (6) consecutive admissions to two city hospitals, to nearly 50% (7, 8). Sarno, Buonaguro, and Levita (9) reported on a group of 125 individuals with closed head injuries admitted to a rehabilitation center. The individuals studied fell into three groups: those with classic aphasia (30%), those with dysarthria accompanied by subclinical aphasia (34%), and those with subclinical aphasia (36%). The authors classified individuals as aphasic if their use of speech for expression and/or reception was impaired. Subclinical aphasia referred to evidence of linguistic processing deficits on formal testing in the absence of clinical manifestations of linguistic impairment. The apparent discrepancies regarding the incidence of aphasia following TBI are difficult to resolve because of the lack of consistency in the descriptions of the individuals with TBI studied, the different aphasia assessment tools employed, as well as the varied definitions of aphasia applied. An examination of specific linguistic deficits following TBI reported in the literature indicates that anomia, difficulty retrieving words, (5, 7, 9–13) and impaired auditory comprehension (7, 9) are the most commonly observed symptoms. Holland (14) noted that there is overlap in these deficit areas between individuals with aphasia and those with TBI, as well as in the associated reading and writing deficits both groups often demonstrate. However, it is the qualitative differences in the naming errors between the two groups which may be most useful in distinguishing between aphasic and nonaphasic responses. Both individuals with aphasia and those with TBI (particularly those in the acute stages) produce circumlocutions and various paraphasias and have reduced fluency in the generation of category-specific words; individuals with TBI, however, demonstrate additional naming errors. For example, they may also produce naming errors related to their personal

situations or make errors of confabulation (i.e., sometimes bizarre responses related to the individual's disorientation). Milton and colleagues (15) have described a system for qualitatively evaluating naming behavior for individuals with TBI. The system permits descriptions of correct responses, and, when responses are incorrect, descriptions of their semantic, phonemic, and other relationships to the target. For example, for the target stimulus "apple" semantically-related responses might include such utterances as: "fruit", "Granny Smith", or "pear". Phonemically-related responses might include such utterances as: "able" or "ubel". Other responses might include such things as "saw" or "We grew them in our backyard".

### **Focal Right Hemisphere Damage**

As noted by Myers (16) it has only been in the last 25 years that the cognitive and communicative deficits associated with the right hemisphere have been considered. As was the case for left hemisphere damage most instances of focal lesions to the right hemisphere are the result of cerebrovascular accidents (CVA). Localization of specific functions related to language processing in the right hemisphere has been a confusing endeavor. Some investigators have observed that the difficulty localizing the component processes involved in maintaining semantic information may be attributable to the involvement of both anterior and posterior cerebral regions and their interconnections (17). Although it is beyond the scope of the present chapter to discuss in any detail the nature of deficits that result from right hemisphere damage (RHD), this section will summarize some of the characteristic features. Generally speaking the range of deficits linked to RHD may be placed into five broad categories (16). The first is attentional deficits which includes problems with: arousal, orientating, vigilance, sustained and selective attention. The next category is neglect which involves a reduction of: attention to left-sided input, use of left limbs, awareness and recognition of left-sided body parts, and awareness of illness. The third category involves visuoperceptual deficits including: visual attention, integration, and memory, and spatial and topographical orientation. A fourth category is affective and emotional deficits including reductions in: the use of facial expression to convey emotion, sensitivity to facial expressions of others, use of prosody to convey emotion, and comprehension of emotional prosody. The final category is cognitive and communicative deficits, included here are reduced: discourse comprehension and production, communicative efficiency and specificity, processing of complex inferences as well as alternative and ambiguous meanings, sensitivity to contextual information, and appreciation of shared knowledge.

With regard to specific linguistic impairments, individuals with RHD typically perform adequately on

language tasks that involve convergent processing (i.e., those requiring a limited number of responses and familiar word meanings) such as confrontation naming, yes/no questions, and providing definitions. Divergent language tasks (i.e., those involving a wide range of meanings which diverge from a single semantic concept such as verbal fluency, open-ended questions, or resolving ambiguities) present more difficulty for this group. They often have trouble understanding intended meanings because of a decreased ability to generate, maintain, or inhibit additional, alternate, and related meanings when the dominant meaning is inappropriate to the context (16).

### **Focal Subcortical Damage**

There is a growing body of literature which documents that right-handed individuals who sustain damage to the left basal ganglia or left thalamus can also develop aphasia (18–20). Three subcortical aphasia syndromes have been described by Naeser and associates. The first, anterior syndrome, results from damage in the internal capsule, lenticular nucleus, and anterior white matter. This syndrome is characterized by hemiplegia; slow, dysarthric speech with near normal phrase length and prosody; poor confrontation naming; good repetition; good comprehension; and poor oral reading and writing. The second is posterior syndrome, which is associated with damage in the putamen and internal capsule, and the posterior white matter. Features of this syndrome are hemiplegia, fluent speech without dysarthria, good single word repetition but poor sentence repetition, impaired confrontation naming, poor comprehension, reading and writing. The third pattern described, anterior-posterior syndrome, results from capsular-putamenal damage with anterior and posterior white matter involvement. Characteristics include a combination of symptoms seen in both Broca's and Wernicke's aphasias. Robin and Scheinberg (21) have cautioned that aphasia caused by lesions in the basal ganglia result in a variety of speech and language impairments that are not all accounted for by the three syndromes described by Naeser and associates.

Aphasia resulting from damage to the left thalamus is typically characterized by hemiplegia and difficulty initiating spontaneous speech. In addition, speech may be echolalic and contain neologistic errors. Fairly good auditory comprehension and reading are usually noted, while writing and word retrieval are impaired. These individuals have also been observed to be perseverative with fluctuating performance moment to moment (22).

### **Diffuse Axonal Damage**

Although individuals with TBI may incur focal lesions, a far more common type of brain pathology following TBI, and specifically closed head injury, is diffuse axonal

injury. This pattern of injury is typically associated with what has been termed confused language (10, 23–25). Confused language is described as receptive/expressive language that may be phonologically, syntactically, and semantically intact, yet lacking in meaning because responses are irrelevant, confabulatory, circumlocutory, or tangential in relation to a specific topic, and lacking a logical sequential relationship between thoughts (26). Such language dysfunction may be mistaken for a fluent aphasia but is more appropriately considered cognitive in nature as opposed to linguistically-based, that is, as a symptom of cognitive rather than linguistic deficits. Traumatic brain injuries frequently result in significant disruption of cognitive processes such as (attention, memory and executive functions). More recent considerations of language disruption following TBI have suggested use of the term cognitive-communicative disorders as being a more accurate description of these impairments. Cognitive-communicative disorders involve difficulty with any aspect of communication secondary to cognitive dysfunction (27). Some individuals with TBI exhibit language disorders most consistent with aphasia, some with communicative deficits comparable to those seen in RHD, and some, particularly in the acute stages of recovery from TBI, demonstrate language behavior consistent with confused language. Regardless, a primary component of language dysfunction in the majority of TBI survivors pertains to disordered language use (i.e., pragmatics). Pragmatics refers to the set of rules which govern the use of language in context (28). Sohlberg and Mateer (29) observed that whereas individuals with aphasia may communicate better than they talk, individuals with TBI appear to talk better than they communicate. Pragmatic deficits are probably most prevalent in those individuals with frontal lobe injuries. Although the frontal lobes are not thought to be responsible for primary cognitive functions, it appears they are involved in coordinating and actualizing many functions involved in cognitive processing such as attention, motivation, regulation, and self-monitoring (30). Individuals with prefrontal injury frequently demonstrate problems, among other things, with: disorganized discourse; inappropriate social interactions (e.g., difficulty interpreting social cues); and abstract forms of language (e.g., irony or sarcasm) (31).

### **DISCOURSE ANALYSIS**

Just as predominant impairments of language caused by focal lesions may mask subtle cognitive disturbances, primarily cognitive disturbances resulting from diffuse brain injury, may mask subtle language deficits (32). Such deficits typically go undetected, or are incompletely delineated by the traditionally used language assessment tools, such as aphasia batteries. In an effort to document such

pragmatic deficits many investigators of verbal communicative ability following TBI have chosen to analyze *discourse* (33–43). Discourse is a series of related linguistic units that convey a message. The length of a given discourse is determined by the communicative function of the message. There are various types of discourse and each type has different cognitive and linguistic demands (44). It has been suggested that discourse is the most natural and basic unit of normal verbal communication (45). Furthermore, accurate production or comprehension of a narrative requires a complex interaction of linguistic, cognitive, and social abilities (i.e., language use) that are sensitive to the particular disruption following TBI.

Discourse analyses begin with the elicitation of a spoken *narrative*, minimally five sentences in length. A variety of types of discourse may be studied including *procedural* (e.g., describing how to change a tire), *descriptive* (e.g., describing a favorite activity), *story narratives*, and *conversational*. The discourse samples are audiotaped and transcribed verbatim. Once transcribed, the narratives are divided into basic units for analysis, such as T-units (i.e., an independent clause plus any dependent clauses associated with it). A T-unit is similar to a sentence but is more reliably identified. Segmenting narratives into sentences is often problematic because of the tendency of some speakers to link sentences of a narrative with conjunctions such as *and*, *or*, and *then*, making it difficult to delineate sentence boundaries (46). Depending on the type of discourse and the focus of the analysis, the actual discourse analysis may be done at a variety of levels (see Table 48-1). For example, in a narrative story, at the sentence level the number of T-units may be tallied as a measure of narrative length, or the number of subordinate clauses may be

counted as a measure of grammatical complexity. Across-sentence analyses may involve examining how speakers link meaning units across several sentences (e.g., counting complete or incomplete ties), referred to as intersentential cohesion. In story narrative analysis, episodes may also be examined. Episode components are defined as information units pertaining to stated goals, attempts at solutions, and consequences of these attempts. Additional analyses include productivity measures such as total words produced or total speaking time, content measures such as accurate or irrelevant content units, and measures of conversational speech, for example, appropriateness of an utterance or topic maintenance.

### DISCOURSE DEFICITS FOLLOWING TBI

Functional communication requires language competence in a variety of settings ranging from informal social interactions to formal educational or work-related tasks (42). Findings of recent investigations have demonstrated that individuals with TBI experience difficulty with communicative effectiveness across a number of discourse genres (see 47–49 for reviews). What follows is a summary of several studies of discourse in individuals with TBI. Prior to beginning, a clarification on the use of the term TBI is offered. Although both closed and penetrating head injuries are classified as TBI, there are distinct differences between the two types, both in terms of array of deficits and recovery, the discussion of which is beyond the scope of this chapter. Throughout the review, which follows, the generic term TBI will be used because in many instances authors have not specified whether the individuals with brain injuries studied, had a penetrating or closed head injury. This review is organized by the level analysis. Prior to beginning this summary a brief overview of the levels of analysis for discourse production is provided. The most basic distinction in the analysis of discourse is whether the discourse genre of interest involves a monologue (narratives such as telling a story) or is interactive in nature (such as participating in a conversation). At the most general level, analyses of narrative discourse are focused on within-sentence processes, termed microlinguistic, or between-sentence processes, referred to as macrolinguistic. Under each of these broad categories are sublevels such as, lexical, syntactic, and lexical-semantic for the within-sentence analyses, and under the between-sentence analyses are the sublevels of local (microstructure) and global (macrostructure). Each of the sublevels has corresponding measures or analyses (see Table 48-1). Conversational analyses can be broken down in terms of the role of the participant during an interaction, that is, whether the individual functions as an initiator or as a responder. In each role there sublevels again with corresponding measures in the analysis.

**TABLE 48-1**  
*Various Levels in the Analysis of Narrative Discourse Production*

GENERAL LEVELS	SUBLEVELS	EXAMPLES OF MEASURES
Within-Sentence microlinguistic	Lexical	Lexical errors
	Syntactic	Completeness Complexity
	Lexical-semantic	Propositional analysis
Between-Sentence macrolinguistic	Local (microstructure)	Cohesion Local coherence
	Global (macrostructure)	Global coherence Story grammar

**TABLE 48-2**  
*Examples of Narrative Story Analyses (Coelho, 2002)*

DISCOURSE MEASURES	DESCRIPTION	EXAMPLE
<b>Sentence Production</b>		
Words per T-unit	Total words in story divided by number of T-units	118 words/6 T-units = 19.7
Subordinate clauses per T-unit	Number subordinate clauses in story divided by number of T-units	3 subord. clauses/6 T-units = .5
<b>Cohesion</b>		
Cohesive adequacy—Percent complete ties of total ties	Each occurrence of a cohesive tie judged as to its adequacy. Number of complete ties in story divided by total number of cohesive ties.	<b>Complete tie</b> – The girl was hungry. <i>She</i> ate her lunch. <b>Incomplete tie</b> – The boys walked home from the mall. <i>They</i> stopped at his house for a snack. <b>Erroneous tie</b> – Dave and Joe drove to the game. <i>He</i> forgot the tickets.
<b>Story Grammar</b>		
Number of total episodes	Total number of complete and incomplete episodes in a story.	<b>Complete episode</b> – <b>[Initiating event]</b> and this fly comes in and the Father's bothered by this. <b>[Attempt]</b> so he decides to swat or hit the fly. and he hits his wife. <b>[Direct consequence]</b> and she goes down. <b>Incomplete episode</b> – <b>[Attempt]</b> and he hits his daughter <b>[Direct consequence]</b> and the daughter goes down to the floor.
Proportion of T-units within episode structure	Number of T-units in episode structure divided by total number of T-units in story.	10 T-units in episodes/ 16 total T-units = .62

### Narrative Discourse

For each of the levels of analysis for narrative discourse a brief description is provided of each analysis followed by a summary of the findings from the TBI discourse literature. Examples of some of the more commonly used narrative analyses appear in Table 48-2. This will be followed by a comparable discussion of the analyses of conversational discourse.

### Microlinguistic Analyses

**Lexical Production** Examinations of lexical production typically involve measures such as lexical diversity (i.e., number of different words produced) and the occurrence of paraphasic errors. The literature on lexical problems in discourse following TBI has been somewhat equivocal. For example some authors have reported a reduction in the number of different words produced (50) or a greater frequency of verbal paraphasias (51) following TBI, while others have noted that lexical production was not a

problem for the individuals with TBI they studied (52, 53). Difficulties with verbal fluency and word retrieval following TBI reported in the discourse literature must be interpreted cautiously. Some of these studies have included, within their participant groups, individuals with TBI who were aphasic (e.g., 37, 51).

**Syntax** Syntactic aspects of discourse have been examined in several studies with mixed findings. Syntactic complexity, as measured by percentage of T-units containing dependent clauses (33), embeddedness of subordinate clauses (51), subordinate clauses per T-unit (54), and words per T-unit (55), was comparable to that of normal controls. Further, syntactic complexity was not judged as being a primary deficit when rated on various pragmatic rating scales (52, 53, 56). By contrast, other investigators have reported syntactic impairments in the discourse of individuals with TBI. For example Campbell and Dolaghan (50) noted that syntactic complexity, as measured by percentage of utterances containing two or more lexical verbs, was decreased in six of nine participants they

studied. In addition an increased incidence of grammatical errors (e.g., omissions of the subject, main verb and other required grammatical morphemes, word order transpositions, verb tense and agreement errors) have also been noted for participants with TBI versus normal controls (51, 57). Once again these findings may have been partially contaminated by the presence of aphasia for some of the brain-injured participants.

*Lexical-Semantic* The contradictory findings, noted for lexical production and syntax, have prompted other investigators to examine the microlinguistic dysfunction in the discourse of individuals with TBI through semantic analyses, specifically propositional analysis. The advantage of propositional analysis is that it permits the examination of semantic complexity of an utterance apart from sentence structure and grammaticality (58). Propositions are meaning units identified with respect to a predicate (i.e., verb, modifier) and its arguments (i.e., agent, instrument). Any sentence may contain several propositions (59). Using a measure of words per proposition, Chapman and colleagues (33) did not find deficiencies in information flow for a group of adolescents with TBI. However, McDonald (39) tallied unspecified propositions in explanations of a board game by two individuals with TBI and found that one participant provided less detail than the non-brain-injured controls. Another study that applied propositional analyses, noted that individuals with TBI appeared to have difficulty with the planning and organization of language (60). Similarly, individuals with TBI were noted to produce significantly fewer propositions per T-unit than normal controls. In other words, they demonstrated a decreased ability to insert multiple ideas into single sentences (61). By contrast, the non-brain-injured (NBI) participants' appeared to chunk information, and that appeared to be a mechanism for linking propositions together, which increased the likelihood that the listener might understand multiple ideas as a connected semantic unit. The participants with TBI appeared less adept at applying this strategy to facilitate discourse organization.

### Macrolinguistic Analyses

Continuing with the review of narrative discourse analyses, the focus now shifts to the macrolinguistic analyses which examine discourse performance between or across sentences.

*Cohesion* Sentences are connected by various kinds of meaning relations described as cohesive markers or ties. A word is considered a cohesive marker if its meaning cannot be adequately interpreted without the listener searching the text, beyond that sentence, for the completed meaning. Cohesional analyses, as described by Halliday and Hasan (45), have been undertaken in several studies of discourse and TBI. Discourse samples of

individuals with TBI have been described as lacking continuity as evidenced by their production of fewer cohesive ties than normal controls in both narrative and procedural discourse tasks (37, 40). However, other investigators have reported that individuals with TBI produced a comparable number of cohesive ties as NBI participants in narrative discourse (39, 51, 54, 62). Differences in the proportional use of ties across discourse tasks have been reported for individuals with TBI (40, 54). Mentis and Prutting observed that their TBI participants used different cohesive patterns which appeared to be related to their reduced linguistic processing abilities, their reduced pragmatic abilities, as well as their attempts to compensate for the linguistic deficits. Liles and colleagues noted that, in a story retelling task, similar proportions of referential (e.g., *Tom is an engineer. He works in Ohio.*), lexical (e.g., *I gave Frank our tickets. The idiot lost them all.*), and conjunctive (e.g., *Bill worked all night. And his hammering kept the rest of us awake.*) markers occurred for both the TBI and NBI groups. In the story generation task however, a distinction between the groups appeared in which the individuals with TBI showed a reversal of the pattern used in the story retelling task. In story generation all of the TBI participants decreased the proportional use of reference and increased the proportion of lexical ties. This shift in the proportional use of types of cohesive ties across the story tasks was attributed to the TBI groups' apparent direct reference to the stimulus picture. These direct references were characterized as interjected descriptors of the picture that were unrelated to the rest of the text. The individuals with TBI rarely integrated these lexical items into the text structure and consequently they were often judged to be incomplete ties. The TBI participants' tendency to refer outside their texts suggested that they were unable to detach themselves from the perceptual salience of the stimulus picture in order to organize their language for story development. In a final study, Coelho and colleagues (35) examined cohesion in discourse samples from a story generation task gathered longitudinally from two individuals with TBI. One individual demonstrated poor cohesive adequacy with meaningful content, as measured by story structure, and the second, fair to good cohesion with poor content. These findings emphasize the clinical utility of monitoring discourse abilities longitudinally and of employing a multilevel analysis procedure.

*Coherence* Coherence refers to the conceptual organization of discourse. The coherence of a text depends on the speaker's ability to maintain thematic unity (63). Coherence is typically considered from two perspectives, global and local. Global coherence pertains to how discourse is organized with respect to a general goal, plan, or topic. Local coherence refers to the maintenance of meaningful conceptual links between individual sentences within a text. Coherence has been specifically examined

in the narrative discourse of individuals with TBI (39, 51, 62) and the findings have been mixed. With the exception that the participants with TBI produced more unexplained references, McDonald (39) noted that their texts were as coherent as those of the normal controls. Similarly, Van Leer and Turkstra (62) found no differences in the coherence ratings for their groups of TBI and NBI participants. However, Glosser and Deser (51) reported that the individuals with TBI they studied were significantly impaired relative to the normal controls in measures of local and global coherence, with global coherence most impaired. These authors suggested that coherence depends on intact access to semantic memory representations of real-world knowledge, as well as perceptual and conceptual integration necessary to maintain the plan and overall organization of discourse. In addition, the ability to produce discourse perceived as coherent requires simultaneous attention and mental manipulation of several bits of information including integration of the speaker's plan and the listener's perspective. The TBI participants' greater impairment with the maintenance of global versus local coherence, suggested that their discourse impairment was more related to a disruption of macro-organizational abilities as opposed to problems with meaning relationships between contiguous concepts (51).

*Story Grammar* Story grammar pertains to the purported regularities in the internal structure of stories that direct an individual's comprehension and production of the logical relationships between people and events. Story grammar knowledge is typically measured by complete episodes. An episode consists of (a) an initiating event that prompts a character to formulate a goal-directed behavior, (b) an action, and (c) a direct consequence marking attainment or nonattainment of the goal. An episode is considered complete only if it contains all three components (64). A variety of difficulties with story grammar has been reported for individuals with TBI. For example, Chapman and colleagues (33) noted that their severely impaired group of individuals with TBI demonstrated a reduction in the number of essential story components, failed to signal new episodes with setting information, and often omitted essential action information. These authors commented that it was unclear whether this difficulty was a reflection of an underlying impairment of the internal story schema or difficulty implementing story schema during discourse production. In another study NBI participants and those with TBI produced comparable numbers of complete episodes in a story-retelling task, but three of the four individuals with TBI produced no episodes in story generation (54). The TBI participants' apparent inability to use episode structure in the story generation task, in spite of having been able to produce complete episodes in the story retelling task, suggested that the story generation task required an interaction of cognition and language use in which the

TBI participants could not consistently engage. A reduction in the number of total episodes produced was also noted in a later study by the same authors (35). Finally, Coelho (65) noted that a group of 55 TBI participants produced fewer T-units within episode structure (i.e., the proportion of total T-units that contributed to episodic structure) than did a group of 47 NBI individuals. Although the TBI and NBI participants were not different in terms of the number of total episodes produced, which had been reported in previous studies (35,54), the NBI participants produced more T-units within the structure of episodes. In other words, the NBI group produced fewer extraneous T-units—that is, T-units that did not contribute to episodic structure. This measure was considered to be an indication of participants' ability to use story grammar as an organizational plan for language.

### *Miscellaneous Measures*

*Informativeness.* The measurement of informativeness in discourse production has focused on three aspects primary aspects: amount of information communicated, quality of information (incompassing such descriptors as irrelevant, redundant, off topic, over personalized, etc.), and efficiency of information (66). The discourse output of TBI participants has been described as reduced in a number of studies as measured by number of words (and/or meaningful words), utterances or sentences; mean length of utterance in morphemes or communication units (comparable to T-units); or some combination of these measures such as number of words per T-unit or syllables per story grammar element, and percentage of syllables or utterances in mazes (33, 37, 42, 50, 55, 65, 67). Individuals with TBI have also been described as comparable to normal controls in terms of the amount of pertinent content expressed and in narrative length, but significantly slower in the rate of information produced (36, 55). These individuals appeared to “talk past the point of diminishing returns”, their oral narratives were lengthier and slower relative to the amount of content provided (36, p. 6). Other investigators have reported normal productivity for individuals with TBI in terms of the number of T-units or sentences in narrative tasks (40, 54).

Other indices of informativeness have included such measures as: number of essential steps included in a description of a procedure (42), amount of pertinent content (36), content units (37), amount of essential information, accuracy of story, and implied meanings (68) and number of concepts introduced (55). In general mixed findings have been noted with essential steps and pertinent content the TBI participants being comparable to the normal controls (36, 42), but in other studies the individuals with TBI produced fewer content units and concepts and demonstrated some difficulty with implied meanings (37, 55, 68).

### *Summary of Findings on Narrative Discourse*

Numerous investigations have illustrated the clinical utility of narrative discourse analyses with the TBI population (33–37, 39, 40–42, 50, 51, 54, 55, 60, 62, 65, 67, 68). In terms of microlinguistic processes, findings on lexical production and syntactic aspects of discourse have been noted to be somewhat ambiguous. Some investigators have reported difficulties in these areas for individuals with TBI, and others have observed that these abilities remain intact following injury. Results from some of these studies have been confounded by the inclusion of individuals who were also aphasic as a result of their TBI. Although some individuals with TBI in the acute stages of rehabilitation may demonstrate impairments with word retrieval and syntax, such discourse deficits are not characteristic of this population in the chronic stages (65). When microlinguistic processes are examined by means of semantic analyses the findings are more straightforward. Individuals with TBI demonstrate consistent problems with the planning and organization of language as reflected in their difficulties inserting multiple ideas into single sentences (60, 61).

Narrative discourse performance has also been evaluated extensively in terms of macrolinguistic processes, namely cohesion, coherence, and story grammar. Cohesion has been noted to be an area of inconsistent impairment and performance may vary considerably depending on the discourse elicitation task presented (40, 54). For example, the cohesive adequacy of individuals with TBI has been reported to be comparable to that of normal speakers in story retelling, but impaired for story generation (54). Similarly, the proportion of types of cohesive ties used by participants with TBI changed from story retelling to story generation, which was not the case for the normal speakers (40, 54). Similar to cohesion, TBI participants' ability to generate complete episodes was frequently effected by the nature of the task, with story retelling being easier than story generation. Story generation required a complex interaction of language and various cognitive abilities that were difficult for even mildly impaired individuals with TBI (54, 65). It has also been noted that TBI participants produced more T-units that did not contribute to episodic structure. It appears that these individuals have difficulty using story grammar to organize language (65). Along similar lines, conceptual organization of discourse (i.e., coherence) has also been noted to be problematic for individuals with TBI. Specifically, their greater difficulty with the maintenance of global (i.e., general plan or goal) versus local (i.e., conceptual links between sentences) coherence suggests a disruption of macro-organizational processes for discourse (51). Analyses of story grammar (i.e., the generation of episodes) and cohesion enable discourse samples to be examined at multiple levels allowing for the delineation of distinct discourse patterns (35).

Finally, the applicability of findings on narrative discourse productivity and content analysis of individuals with TBI have also been limited by the inclusion of individuals with aphasia and dysarthria in the groups studied. However, in general terms, the TBI participants studied demonstrated decreased discourse efficiency, generating information at a slower rate in lengthier utterances than controls (36, 55).

### **Conversational Discourse**

The analysis of conversational discourse is of particular interest for the study of the TBI population because of its importance in the process of socialization. The development and maintenance of social relationships has been noted to be challenging for survivors of TBI. The consequences of this difficulty are social isolation, increased reliance on family for social support, and significant problems returning to work, school, and premorbid avocations. It has been suggested that these interactional problems are the result of social skills deficits, and that these deficits in social skills are felt to be a reflection of subtle impairments in pragmatic language use during conversation (69, 70). There have been numerous reports pertaining to the analysis of conversational discourse following TBI. These reports are summarized below by type of analysis.

#### *Response Appropriateness*

The appropriateness of TBI participants' utterances within conversations utilizing procedures described by Blank and Franklin (71) has been described (72, 73). A greater number of turns per conversation were noted for the participants with TBI than for the normal controls. This increased number of turns resulted from their shorter length of utterance per turn and their conversational partner's higher percentage of oblige production (i.e., utterances for which a response is expected, as in a question) (72). In a follow-up to the original study, which involved 5 individuals with TBI, Coelho and colleagues (73) studied 32 individuals with TBI, all of whom had recovered a high level of functional language, and were all rated as Rancho Los Amigos Level of Cognitive Functioning (74) VII (automatic-appropriate) or above. As a group the individuals with TBI did not initiate a great deal and appeared dependent on the examiner to maintain the momentum of the interaction. They produced fewer spontaneous obliges and comments (i.e., utterances for which a response is not required) than did the NBI controls and functioned primarily as "responders". Further, when they did respond, they provided more information than was requested. Although this extra information was not inappropriate or bizarre, it did not facilitate disclosure on the part of the conversational partner. The function of disclosure in social interaction is to allow the opportunity to

talk about oneself or subjects of interest to oneself, in order to establish, sustain and enjoy social interaction (69).

### *Analysis of Topic*

The proficiency by which participants manage conversational topics is critical to the success of an interaction. Topic management pertains to how participants in a conversation extend or maintain a given topic, as well as how discussion of a topic is discontinued, and how and when participants change topics (75). The specific contribution of speakers and their conversational partners to topic maintenance and development through analysis of ideational intonation units has been examined (76). Ideational describes a concept borrowed from Halliday (77) and pertains to the idea that discourse is about something or contributes some content. Therefore, ideational units can be assumed to represent what speakers contribute to topic maintenance and development, and to exist as a function of cognitive processes. For example, there are categories of ideational units for new information appropriate to the topic contributed by a speaker and categories representing no new information but still maintaining a topic. Thus it is reasonable to assume that production of ideational intonation units is likely to be disrupted in persons with brain injuries and cognitive impairments. Mentis and Prutting (76) found differing patterns of production between an adult with TBI and a NBI control in their intonation unit analysis across unspecified, concrete, and abstract conversational contexts. The individual with TBI produced fewer units containing novel information not specifically requested, fewer clarification and confirmation requests, and more agreement and acknowledgement units. In a follow-up study this analysis procedure was applied to conversational samples of a group of ten individuals with TBI and ten NBI controls (78). The intonation unit analysis did not distinguish high functioning individuals with TBI from controls matched for age, gender, and socioeconomic status. The method of eliciting conversation, with the examiner directing the conversation, may have constrained the context and, thereby, masked deficits commonly attributed to this population's difficulty in social interchanges.

Other approaches to the analysis of topic management have involved the examination of how topics are introduced and changed during a conversation (73, 79). Any participant in a conversation may introduce topics. Topics are changed in one of three ways: (a) at the beginning of the conversation, or by ending discussion of one topic and initiating another, referred to as a novel introduction; (b) by means of a smooth shift, in which discussion of one topic is subtly switched to another; or (c) by means of a disruptive shift, in which discussion of one topic is abruptly or illogically switched to another

topic. Findings on this measure have been mixed. Coelho et al. (79) observed that five individuals with TBI demonstrated difficulty initiating and sustaining topics compared to five matched controls. However, when a group of 32 individuals with TBI were compared to an NBI group of 43 individuals, the group with TBI produced comparable numbers of Novel Introductions and Smooth Shifts as the NBI group during their conversations with an examiner. Neither group produced many Disruptive Shifts (73).

### *Systemic Functional Linguistics*

Systemic Functional Linguistics (SFL) describes language use as a series of choices (77, 80). When a speaker produces an utterance, choices are made pertaining to what will be said and how it will be said. The listener and the situation in turn, influence the what and the how of the utterance. The impact of context on language use is an important consideration of SFL. Context has been described as a combination of three components: field, mode, and tenor. Field pertains to the nature of the social interaction taking place (e.g., a speech or a conversation with friends). Mode refers to the modality by which the discourse is produced (e.g., written or oral). Tenor describes who is involved in the interaction, their relationship to each other, and their roles or status (e.g., teacher and student, two strangers, clerk and customer) (43). Two additional components of SFL are genre, which pertains to the influence of culture on language (i.e., the step-by-step structure that are followed to achieve goals) and ideology, which involves the participants' biases and personal perspectives. Three types of SFL analyses have been used to study the nature of language structures, which are used to establish and maintain interpersonal interactions of individuals with TBI. These have included: exchange structure analysis, generic structure potential, and mood and modality analysis. Each of these is described briefly below.

Exchange structure analysis. Exchange structure analysis (ESA) involves the examination of who has the knowledge (i.e., the primary knower) in an interaction and how that information is transferred (to the secondary knower). This approach has been applied to interactions of individuals with TBI during a variety of service encounters (e.g., calling about: bus schedules, getting a driver's license, therapy schedules, and therapy goals) (43, 81, 82). Investigators studied whether TBI participants and NBI controls altered their communicative behavior with different conversational partners who varied in terms of familiarity (e.g., an information operator, a policeman, their mother, or a therapist). In reviewing the findings from this analysis the authors examined the communication partners' responses to the TBI versus control participants. Results indicated that the therapists gave more



information to the normal controls than to the TBI participants. The mothers tended to provide more information to their NBI sons than to their sons with TBI, but this difference was not significant. In terms of requesting information therapists asked more questions of the normal controls than of the individuals with TBI, while the police asked more questions of the TBI participants than of the NBI individuals. Finally, therapists generated more clarifications and checking utterances with the individuals with TBI than with the NBI group. There were no other significant differences for the communication partners. In comparing the individuals with TBI to the NBI controls across the four conditions a number of significant differences were reported. First of all the TBI group produced more information in the police encounter than did the control group. Some of the information offered was inappropriate (i.e., more information than was requested, which was similar to the findings of Coelho and colleagues (72, 73)). The individuals with TBI provided more information in their interactions with the police than in those with the therapists and the operators at the bus station. This was felt to be due in part to the greater number of questions produced by the police. Because the mothers did not request much information from their sons with TBI, that group provided less information to their mothers as compared to the NBI group. In addition, the TBI group requested more information from the therapists than did the controls. The individuals with TBI generated more requests for clarifications than the NBI groups when conversing with the therapists. Finally, the TBI group asked for clarifications more with the police than with their mothers or the operators at the bus station (81, 82). Overall, results indicated that the discourse performance of the participants with TBI varied according to their conversational partner.

Generic structure potential analysis. This analysis addresses the issue of which aspects of language use appear to be influenced by particular dimensions of the context. Togher and colleagues (82) examined the core structural elements (e.g., greeting, address, service initiation, service request, service compliance, close, goodbye, etc.) that would be expected in two types of interactions (i.e., the bus information operator, and the police) for TBI and NBI participants. Results indicated that the generic structural elements in the TBI service encounters were different in terms of length and content than those of the controls. The TBI group had difficulties opening sequences and with the main service requests. This group also produced repetitious and at times inappropriate elements not seen with the NBI group. There were several significant differences noted between the police and bus information encounters as well. When the control participants interacted with the police the greeting sequences were shorter and promptly followed by succinct service requests. In addition the closing/goodbye sequences were

longer when they spoke to the police than when they interacted with the bus information operator. By contrast, when the participants with TBI interacted with the police they had longer greeting sequences and shorter goodbyes (82). The authors comment that opening and closing sequences facilitate the development of interpersonal relationships by establishing credibility, confirming the success of the encounter, and encouraging future contact. During the longer closing sequences of the NBI participants, the police encouraged them to call again, however this was not observed during the shorter closing sequences of the TBI group. This analysis of the overall structure of an interaction facilitates the identification of specific structural elements that may be problematic. These can then be further analyzed in terms of mood and modality.

*Mood and Modality Analysis* The analysis of mood may be used to study the lexical and grammatical choices made at the clause level to establish the degree of directness being expressed (e.g., statements such as "I will be home on Tuesday" are direct, whereas a declarative statement with rising intonation such as "You'll be home Tuesday?" are less direct and considered to be more polite). A direct statement may be either positive or negative (e.g., "I will be home" or "I won't be home"). Between these two poles a speaker may indicate uncertainty or directness through expressions of modality such as *might*, *must*, *possibly*, *probably*, or comments such as *I think*. Definiteness decreases as the speaker's expression of modality increases. Mood and modality has been examined in the interactions of TBI and NBI speakers in four interactions (with: a bus information operator, police, mother, therapist). Results indicated that the TBI participants were able to access a variety of politeness strategies, however they appeared less adept at applying these strategies across the four different interactions when compared to the NBI group (83).

### *Conversation Analysis*

Other highly structured analyses have also been applied to conversational samples. One such system is conversation analysis (CA) which was developed to delineate the structural organization and sequential ordering of talk. Friedland and Miller (84) have applied CA to conversational samples of an individual with TBI. The authors commented that CA was sensitive for identifying pragmatic deficits in this individual. Specifically it identified the precise locale of conversational breakdowns and how these were repaired or not. Further, it demonstrated how one conversational partner adapted to these breakdowns and was successful during interactions with the TBI participant and another was not.

### *Pragmatic Rating Scales*

In contrast to the very structured analysis procedures of SFL and CA a number of investigators have utilized

pragmatic rating scales to investigate conversational abilities (56, 85–90). Although some of the pragmatic dimensions rated within these scales are redundant, each scale has a rather novel approach to looking at conversation. For example, some scales rate both nonverbal (e.g., intonation, facial expression, eye contact, gesture) and verbal (conversation initiation, turn taking, topic maintenance, response length, presupposition and referencing) communication (87). While others focus on specific aspects of the verbal message such as intelligibility, sentence formation, and coherence of narrative (56). Some theoretically-based scales focus on aspects of pragmatics such as utterance acts (e.g., vocal intensity, voice quality, prosody), propositional acts (e.g., lexical selection, word order, stylistic variations), and illocutionary and perlocutionary acts (e.g., speech acts, topic, turn taking) (88). Other scales are questionnaires completed during an observation or from personal knowledge which deal with such issues as “Does client: make rapid and inappropriate changes in conversational topic without clues to the listener? or fail to attend to cues for conventional turns, interrupting frequently or failing to hold up his or her end of the conversation?” (85, 91). Observations on the use of such pragmatic rating scales for assessing individuals with TBI have been generally positive. The scales are not labor intensive, which is the case for most of the other formal analysis procedures, and they are useful for assessing selected communicative behaviors unobtrusively, in real-world settings.

### *Social Information Processing*

A final category of analysis views communication as an integral aspect of social pragmatic skills. A universally accepted definition of social skills is absent from the enormous literature on this topic. Similarly, numerous conceptual models of social skills have been described (92). The ability to communicate effectively is the basis of socially skilled behavior, and in humans, language is the primary method of communication. Ylvisaker, Urbanczyk, and Feeney (93) suggested a conceptualization of social skills following TBI that specifically incorporated the dimension of communication. Five components are included: (a) the individual’s knowledge of self; (b) the extent to which an individual attends to their personal appearance; (c) social cognition (i.e., social perception, social knowledge, and social decision making); (d) communication, and (e) the social environment (i.e., significant people in the individual’s natural environment). Analysis procedures pertaining to social cognition have examined such skills as cooperation, turn-taking, politeness, negotiation, topic management, and sensitivity to role and status of all participants. For example, McDonald (39) studied two individuals with TBI and 12 NBI participants explaining a novel procedure to a blind-folded

third person. The productions of the TBI participants were rated as disorganized, confusing, and ineffective as compared to the controls. The disorganization was attributed to errors in sequencing and inclusion of irrelevant propositions. In a second study individuals with TBI and NBI controls participated in a barrier task, which required that the participants explain a board game to a listener not present in the room (94). The authors noted that the TBI participants appeared to be bound to the physical properties of the stimulus before them, and omitted important details from their explanations that the listener needed to understand the game. Similar findings were noted for adolescents using the same task (95). The investigators concluded that overall performance was limited by the TBI participants’ decreased ability at role taking which in turn was associated with frontal lobe damage. In a final study, Turkstra and colleagues (96) studied social cognition of 10 adolescents with TBI and 60 NBI peers. Two tasks were presented: emotion recognition and conversation judgment. In the emotion recognition task, the participants were asked to identify the emotion depicted by an actor (happy, sad, peeved, angry, disgusted). For the conversation judgment task, six conversation skills were depicted: (a) attentive listening; (b) perception of nonverbal cues; (c) detection of sarcasm; (d) sharing the conversational burden; (e) humility; and (f) speaking at the listener’s level. Each participant was asked to make judgments about the actor during videotaped vignettes (e.g., “Is the person a good listener?”, “What makes you think so?”). Results indicated that the TBI group differed significantly from the NBI group for both recognition of emotion and the conversational judgments. Most of the errors on the conversation skills task were related to the detection of sarcasm and the feelings it might evoke in a listener. This finding was consistent with those of McDonald (97) which demonstrated impaired understanding of sarcasm and other forms of social inference in adults with TBI.

### *Summary of Findings on Conversational Discourse*

The analysis of conversational discourse has been conducted from a variety of perspectives and the procedures applied have ranged from rating scales or check lists to highly structured analysis protocols. Although not entirely consistent, results from various pragmatic rating scales, and analyses of response appropriateness and topic management suggest that individuals with TBI experience difficulty when called upon to function as a partner in communicative dyads, whether in conversation or referential communication. These individuals demonstrate problems initiating and sustaining topics in conversation and frequently rely on their discourse partner to assume a greater proportion of the communicative burden to ensure a successful interchange of information (39, 56, 72, 73, 76, 91).

The role of individuals with TBI as participants in conversational dyads will vary according to the tenor relationships. In addition, the factors of familiarity and status appear to influence the language choices made by conversational partners during these interactions. These language choices are the result of the different roles the conversational participants assume and how conversational partners respond to the disability of the participant with TBI (43).

Finally when conversation is considered as a component of social skills or social cognition, a decreased ability for role taking has been identified as a primary deficit for individuals with TBI. Problems with the recognition of emotion and interpretation of sarcasm and inference also compromise their social functioning (96, 97).

### INTERPRETATIONS OF DISCOURSE DEFICITS FOLLOWING TBI

The present review has indicated that individuals with TBI frequently demonstrate discourse impairments. These difficulties cross discourse genres and are revealed by a variety of discourse analyses. This chapter has focused primarily on descriptions of narrative and conversational discourse deficits. If it is assumed that these types of discourse are different in terms of underlying requisite processes, then the reasons for difficulty with narrative and conversational discourse should also be different. What follows are interpretations of narrative and conversational discourse impairments following TBI.

#### Narrative Discourse Impairments

Kintsch and van Dijk (98) have proposed that semantic information may be represented at multiple levels. These levels include: the surface structure, the text base; consisting of the microstructure (i.e., meaning contained in words and phrases) and macrostructure (i.e., topic- or gist-level information), and the mental model where the listener constructs a representation of the situation described (i.e., comprehends the text). The notion that a text's representations occur at a number of levels implies that discourse analysis must be performed at multiple levels as well. The primary division in such structural analyses occurs between the analysis of linguistic (e.g., lexical, syntactic, and cohesion analyses) and of conceptual or semantic representations (e.g., propositional and frame [i.e., higher level of semantic structure specifying constituents and relations among constituents]) levels (99). Two broad types of cognitive functions, assumed to be involved in discourse processing, further characterize these levels of analysis, that is whether an analysis is micro- or macrolinguistic in nature. Microlinguistic functions are language-specific procedures for processing

phonological and syntactic aspects of single words and sentences in the absence of context. Macrolinguistic functions involve cognitive procedures for integrating linguistic and nonlinguistic knowledge for the purposes of maintaining the conceptual, semantic, and pragmatic organization of discourse. The critical distinction between these two categories is that the macrolinguistic processes involve analyses of language units as contextual events (63).

With regard to microlinguistic analyses, the TBI participants have been noted to have comparable scores to normal controls on measures of lexical diversity (100) and syntactic complexity (65). For measures of macrolinguistic processes, no consistent differences between the groups have been noted for cohesive adequacy, however TBI participants typically have lower scores on measures of story grammar performance than normal controls (65). In addition, individuals with TBI demonstrate lower propositional density scores (61). As a group TBI participants demonstrate relatively preserved microlinguistic discourse functioning. The impairments noted in their narrative discourse production are associated with problems in macrolinguistic functions, that is, with the interaction of linguistic and conceptual structures. The finding that the TBI participants present with predominantly macrolinguistic discourse deficits is consistent with the diffuse pathology associated with TBI and closed head injury in particular. Glosser and Deser (51) have specified that microlinguistic, language-specific, functions are dependent on the integrity of a specialized neural system within the left hemisphere. Conversely macrolinguistic functions depend on different neural systems that are non-focal and bilaterally distributed.

To better understand how macrolinguistic discourse functions are disrupted in TBI, Huber's (101) description of text processing may be considered. Two distinct modes are involved: macroprocessing in which the speaker focuses primarily on the critical ideas in a text, and microprocessing in which the speaker deals with individual meaning units and their relationships as conveyed by various syntactic devices. Microprocessing requires linguistic knowledge and an algorithmic processing mode that is rule governed facilitating the analysis of linguistic elements. Macroprocessing involves general world knowledge and pragmatic reasoning and the mode of processing is heuristic. Lexical information, such as key words and idioms, is picked from the text and matched with experiential knowledge and expectations about persons, events, and situations. As soon as a plausible match is obtained, the interpretation process ends (101). This macroprocessing mode is the likely source of narrative discourse breakdown among the group of TBI participants reported on above (61, 65, 100).

There are a variety of cognitively-based explanations for this breakdown that are also reasonable avenues to pursue in future studies of narrative discourse following

TBI. First, optimal discourse processing involves simultaneous micro- and macroprocessing. However, such processing will be hindered by limitations of working memory, potentially resulting in incomplete integration or understanding of all propositional elements within a text. Previous findings of significant correlations between working memory and linguistic cohesion in discourse of individuals with TBI support this notion (37). Other investigators have also emphasized the critical role working memory plays in discourse (102–105). Secondly, individuals who are proficient at discourse processing are able to integrate prior real-world knowledge to facilitate interpretation of the ongoing discourse. This integration of prior experiences is facilitated through the use of story schemas and script knowledge. Schemas and scripts are cognitive structures that generate expectations about the way a story might progress and organize the understanding of real-world events and their consequences. Both scripts and story schemas are attempts to characterize prerequisite memory representations of contextual information. Inclusion of irrelevant information during the production of discourse may reflect attentional or memory problems (106). Finally, the formation of story macrostructure requires knowledge about goals and actions, difficulty with story grammar may reflect problems with executive functions or goal-directed behavior in general. The relationship between executive functioning and discourse would appear to be quite logical. It has been suggested that discourse proficiency involves an interaction of cognitive and linguistic organizational processes, which requires executive control (107). Recent findings have demonstrated several significant, but modest, correlations between scores from the Wisconsin Card Sorting Test (WCST) (108, 109), a purported test of executive functioning, and measures of story narratives (65). This relationship between executive functioning and narrative discourse production in adults with TBI corroborates findings of previous investigations (68, 110).

### **Conversational Discourse Impairments**

The complexities of conversational discourse have been well described in a number of studies (43, 49, 111–113). Effective participation in a conversation is dependent on a variety of factors such as: topic maintenance, turn taking, appropriate referencing, sensitivity to the conversational partner, and general cognitive abilities such as attention, vigilance, and memory. Social cognition (i.e., social: perception, knowledge, and decision making) will also have important influences on conversational skill. Galski and colleagues (114) have commented that the success of an individual's social, vocational, familial, and academic integration rests on the recovery of effective communication.

Although individuals with TBI demonstrate difficulty with many narrative discourse tasks, conversational

discourse appears to be more difficult for this population. This may be attributed to the interactive nature of conversation. Consistent with this explanation, is the report that individuals with TBI produced more discourse errors in conversation than in a structured referential communication task. The authors suggested that conversations are more complex because due to social aspects, such as the relationship between conversational partners that is, familiarity, status, and role, as well as the face-saving strategies used for politeness when communication breakdowns occur (115). Such factors typically are not at issue in non-interactive types of discourse. Additional support for the contention that conversation may be more challenging than narrative discourse for individuals with TBI comes from a study which entered measures of both narrative and conversational discourse into a discriminant factor analysis (DFA). The goal was to determine which type of discourse analysis would best discriminate TBI from NBI participants. Results of the DFAs run with both sets of discourse data indicated that the conversational measures were most accurate in discriminating the groups (116). It appears that because the conversational measures were pragmatic in nature and more sensitive to the communicative dysfunction displayed by individuals with TBI than the more structurally focused narrative measures.

An additional explanation pertains to the potential cognitive factors that have been suggested to be important for meaningful participation in conversation. For example, topic maintenance and appropriate referencing requires both selective and sustained attention. Further, functional memory is required to recall what the speaker has said as well as the listener (112). Social competence requires the ability to apply social skills flexibly in accordance with the rules of an interaction. It has been argued that the inability to flexibly apply behavior according to rules, which entails executive functioning, may account for conversational difficulty following TBI (70). Support for the notion that executive functioning may be an important factor in conversational proficiency comes from findings of significant correlations between measures of conversational performance and scores from the WCST (117). Finally, comprehension of sarcasm and implicit language may also influence the effectiveness of a conversational participant (97).

### **CONCLUSIONS**

This chapter has reviewed the nature of language dysfunction following TBI. Although some individuals with TBI will demonstrate aphasia, most will present with language deficits that are cognitively-based versus linguistic, referred to as cognitive-communicative impairments. The majority of these individuals will present with pronounced difficulties with pragmatics, that is with the use

of language in context. These pragmatic deficits are not readily apparent when the assessment of language is focused on single words or isolated sentences. Rather, language should be evaluated in terms of discourse. Discourse permits the analysis of language at multiple levels (i.e., micro- and macrolinguistic, micro- and macroprocessing) which may be differentially impaired after TBI. Further, the analysis of interactive discourse (i.e., conversation) will reveal difficulties with social cognition that cannot be observed in the typical acontextual assessment settings.

Most survivors of TBI will demonstrate a variety of narrative and conversational discourse deficits. The underlying bases for these impairments are probably different but in many ways similar as well. Problems with narrative discourse are attributed to disruption of macrolinguistic processes involved in the organization of semantic information. This organizational process more than likely involves executive control. Meaningful interactions involve the flexible application of social rules which is also associated with executive functions. Delineation of the processes which subserve discourse will provide important treatment implications for cognitive-communicative impairments.

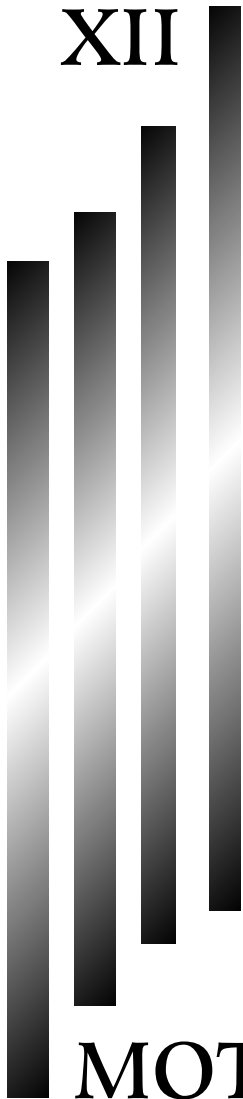
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XII



**MOTOR RECOVERY,  
FUNCTIONAL MOBILITY,  
AND ACTIVITIES OF  
DAILY LIVING**



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# 49

## Neuroscientific Basis for Occupational and Physical Therapy Interventions

*Randolph J. Nudo*  
*Numa Dancause*

### INTRODUCTION

The field of neurorehabilitation is currently undergoing a fundamental change in approach to therapy after central nervous system injury. In the past, occupational and physical therapy after stroke or traumatic brain injury (TBI) was based almost exclusively on empirical data and without a full understanding of the neural processes or correlates of recovery mechanisms. Since the early 1980's, experimental data has been accumulating to provide compelling evidence that the adult brain is capable of significant anatomical and physiological plasticity. These data have contributed to a renewal of the long-debated theory of vicariation, or the taking over of function of damaged brain regions by spared, healthy regions. It has become clear that in both humans and in experimental animal models, the injured brain compensates in a variety of ways that contribute to the spontaneous return of function, and that behavioral interventions are perhaps the most powerful modulators of post-injury plasticity.

Based on this growing evidence for behaviorally-driven neural plasticity after brain injury, and the increasing number of scientists and clinicians that have begun to design therapeutic approaches grounded in the latest neuroplasticity principles, some have suggested that we are fast approaching an impending paradigm shift in neurorehabilitation therapy (1). In the coming years, advances

in behavioral principles, robotics, pharmacotherapeutics, brain imaging, genetics, genomics, nanoelectronics, and neural prosthetics are likely to change the landscape of functional restoration after brain injury. The purpose of this chapter is to introduce the reader to the underlying principles of functional brain plasticity and how they may be applied to restoration of function after brain injury. What circumstances gave rise to the fundamental changes in emerging therapeutic principles? What factors modulate brain structure and function in the healthy and injured brain? How can contemporary therapeutic interventions be improved based on principles of neural plasticity? What does the future hold for further development of therapeutic approaches? While the answers to these questions are still fragmentary, it is hoped that this chapter will help to prepare students and practitioners of neurorehabilitation for the paradigm shift that is already in progress.

It is important to note that most of the clinical examples and animal models of plasticity are based on recovery after ischemic infarct, rather than on TBI *per se*. This is primarily because the vast majority of the literature on post-injury plasticity associated with recovery focuses on stroke or ischemia. In many ways, post-stroke plasticity is an easier phenomenon to investigate and understand. The injury is typically focal and well-circumscribed. The surviving cortical and subcortical tissue is essentially

undamaged. In TBI, injuries may be diffuse or multi-focal. Whether these same plasticity principles based on post-stroke recovery generalize to TBI is still an unanswered question. However, the description of the various modulators of post-stroke plasticity and their neuroanatomical and neurophysiological bases provides a fundamental understanding of the potential for the role of neuroplasticity in post-TBI recovery.

### MATURATION OF OUR UNDERSTANDING OF BRAIN PLASTICITY AND RECOVERY PRINCIPLES

The modern era of the application of brain plasticity principles to recovery after injury began in the mid-1980s with

a series of experiments demonstrating use-dependent modulation of the functional organization of somatosensory cortex (2–6). These studies demonstrated that after amputation of a digit or transection of a peripheral nerve in experimental animals, the deafferented cortex quickly became responsive to inputs from adjacent skin surfaces. While later studies eventually showed that these functional alterations could be attributed, in part, to modulation of pre-existing divergent connections in the lemniscal pathway (such as diverging thalamocortical arbors), other changes, such as alterations in local cortical circuits and long-term anatomical changes have also been reported within the cortex, thus making it clear that the functional organization of the cerebral cortex is modifiable (Figure 49-1).

Results demonstrating use-dependent (and skill-dependent) modulation of auditory cortex, visual cortex,

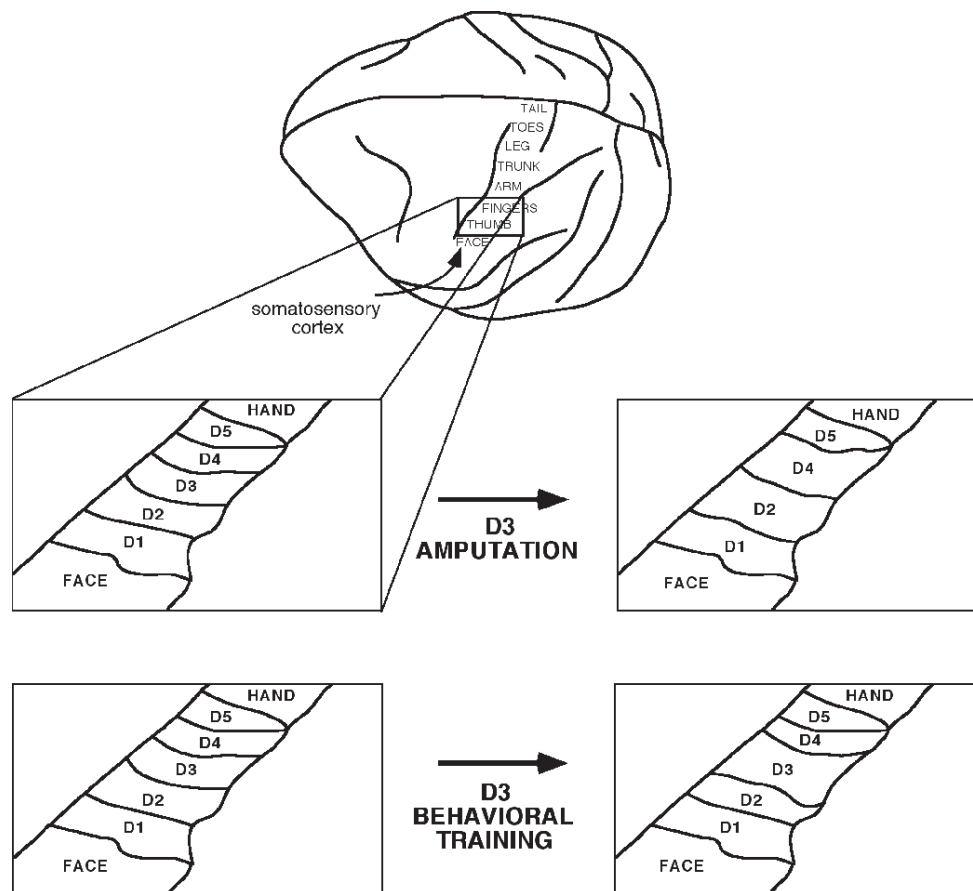


FIGURE 49-1

Classic neurophysiological studies in primary somatosensory cortex (area 3b) of non-human primates demonstrating that the functional topography of cerebral cortex is modifiable after peripheral injury and after repetitive use. Top experiment shows the area 3b hand map before and a few months after amputation of a single digit. Prior to the amputation, area 3b displays the normal topographic pattern, with neurons responding to light touch on individual digits progressing from ulnar to radial aspects of the hand as a microelectrode is introduced from more medial to more lateral locations. Each digit's representational territory in cortex is demarcated by a sharp border. After a digit 3 amputation, neurons in the former digit 3 cortical territory become response to stimulation of skin surfaces adjacent to the missing digit, i.e., to stimulation of digits 2 and 4. Adapted from (2, 6). Bottom experiment depicts changes in the digit 3 representation in area 3b following several weeks training on a sensorimotor task in which digit 3 is repetitively stimulated. The representation of the stimulated digit expands and receptive field sizes become smaller (132)

and motor cortex eventually erased any lingering doubts that topographic plasticity may be a methodological epiphenomenon, or specific to only certain portions of the cerebral cortex. Behavioral improvement appeared to correlate with neurophysiologic map plasticity, suggesting that these changes were an adaptive response of the cerebral cortex to novel behavioral requirements.

However, even in the early 19th century, clinicians and scientists began to ask specific questions regarding brain plasticity, though their knowledge of underlying neuronal mechanisms was rudimentary. While better known for his study of phrenology (with Gall), Johann Spurzheim wrote that brain and muscles can increase with exercise “because the blood is carried in greater abundance to the parts which are excited and nutrition is performed by the blood”. In the mid-19th century, Jean-Pierre Flourens, one of the first experimental brain researchers, asserted that after restricted lesions of the cerebellum, recovery could occur as the result of compensation by other brain areas. This view was later to be incorporated in Lashley’s principle of equipotentiality that states that all parts of the neocortex (or at least, all parts within a localized functional area, such as visual cortex or somatosensory cortex) play an equal role in memory storage, or in a particular physiological function (7).

Several other investigators took up the question of brain recovery mechanisms throughout the first half of the 20th century, including Sherrington, Franz, Glees, Denny-Brown, Kuypers and others using behavioral and neurophysiological techniques (8–13). But it was in the final two decades of the century when solid evidence from experimental animal models accumulated to give adequate credence to the notion that cortical functions are not static in adulthood (14). Parallel human neuroimaging studies confirmed that these same processes could probably be generalized to humans (15).

Thus, the recent intensive interest in recovery after brain injury has come about as a result of two nearly simultaneous events: 1) the maturation of our understanding of brain plasticity principles, and 2) the rapid development of sophisticated neuroimaging techniques. In addition, specifically with regard to stroke recovery, interest has been spurred by the initial effectiveness of pharmacologic and physiotherapeutic interventions introduced during the acute or chronic stages after stroke (i.e., thrombolytic agents, amphetamine, constraint-induced movement therapy) (16–18). These recently developed interventions were largely based on neuroscientific and behavioral principles developed from animal models of post-injury recovery.

While results demonstrating neuroplasticity in healthy brains as a result of experience, and in injured brains as a result of trauma or stroke were largely phenomenological in the initial stage of discovery, the molecular and cellular mechanisms regulating these events are now

being investigated intensively. The coming decade will be important in defining which of the many potential features of neuroplasticity represent adaptive mechanisms, which represent maladaptive mechanisms and which are epiphenomenal.

## NEURAL CORRELATES OF SKILLED MOTOR CONTROL

Because many of the same underlying adaptive neurological processes are thought to occur in both normal and injured brains, to appreciate the events that shape anatomical and physiological plasticity and promote functional motor recovery after brain injury, it is first necessary to understand how repetitive use and motor skill acquisition modulate the structure and function of the normal, uninjured brain. In this section, the organization of the motor cortex will be reviewed briefly. Then, the modulatory role of sensorimotor behavior will be discussed.

### Organization of Motor Cortex

The motor cortex is composed of a number of interconnected cortical regions that are distinguishable from surrounding areas primarily on the basis of cytoarchitecture, thalamocortical and intracortical connectivity (hodology), and electrophysiological properties. In addition to the extensively studied primary motor cortex (M1) located in the precentral gyrus, there are several other motor areas that play important roles in motor control. These include the premotor cortex (dorsal and ventral premotor cortex, or PMd and PMv, respectively), the supplementary motor area (SMA), and the cingulate motor cortex (CM). Each of these motor regions can be further subdivided based on histochemical, hodological and neurophysiological properties (Figure 49-2).

The primary pathway through which the motor cortex directs motor commands to the spinal cord motor neurons is the corticospinal tract. Corticospinal neurons originate from each of the cortical motor regions in the frontal cortex, i.e., from CM, PMv, PMd, SMA and from M1. Additional corticospinal neurons originate from parietal cortex, though their precise function in motor control is still unclear. Monosynaptic corticomotoneuronal neurons (i.e., neurons with somata located in cerebral cortex with fibers terminating directly onto motor neurons in the spinal cord) are thought to originate primarily from M1.

Each of the cortical motor areas is reciprocally interconnected with the others, though to varying degrees. Thus, M1 receives input from premotor, supplementary motor and cingulate motor areas, and emanates corticocortical axons to terminate in these same regions. In addition, cortical motor areas receive substantial input from

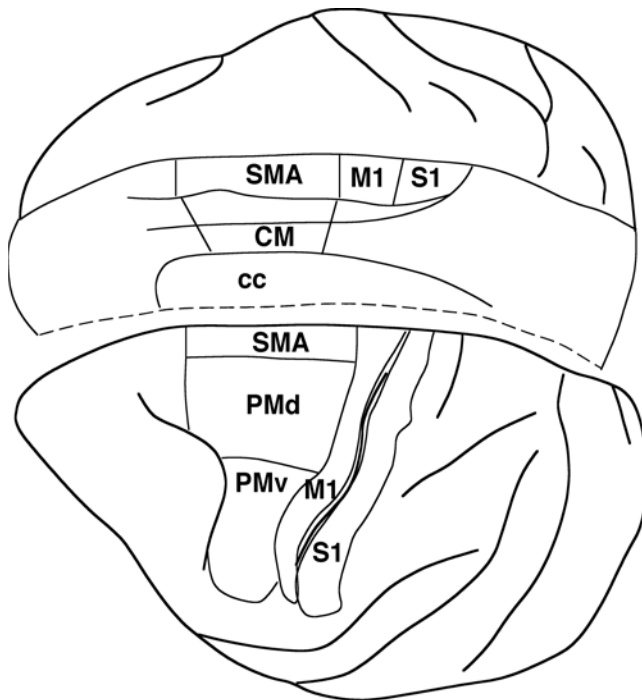


FIGURE 49-2

Location of motor areas in the cerebral cortex of a macaque monkey. At least five subdivisions can be recognized on the basis of structural and functional properties. These include the primary motor cortex located in the precentral gyrus (M1), the dorsal and ventral premotor cortex located anterior to M1 (PMd and PMv, respectively), the supplementary motor area located medial to PMd on the medial aspect of the cortex (SMA) and the cingulate motor areas located in the cingulate gyrus on the medial wall (CM). Each of these main motor areas can be subdivided further based on cytoarchitectonic, neurophysiologic, and chemoarchitectonic criteria. Note that much of the M1 representation is buried in the central sulcus (i.e., on the anterior bank of the precentral gyrus) in most primates (including humans). Thus, access for detailed neurophysiological mapping studies is limited. Certain non-human primate species (e.g., squirrel monkeys, marmoset monkeys) possess a relatively shallow central sulcus allowing more access to the posterior aspect of M1

parietal cortex, specifically from somatosensory regions. Thus, the motor cortex cannot be considered strictly as a motor structure, but instead, is a site of somatosensory-motor integration, with a primarily motor output function based on its corticospinal connections, primarily its monosynaptic connections with motor neurons. In fact, when focal ischemic lesions are made in either the primary somatosensory cortex (S1) or M1 of non-human primates, deficits are quite similar when performance on sensorimotor tasks is assessed (17, 18). For example, in addition to a decrement in manual skill, monkeys with lesions in either S1 or M1 display a type of sensory agnosia. The sensory agnosia eventually subsides, possibly due to the

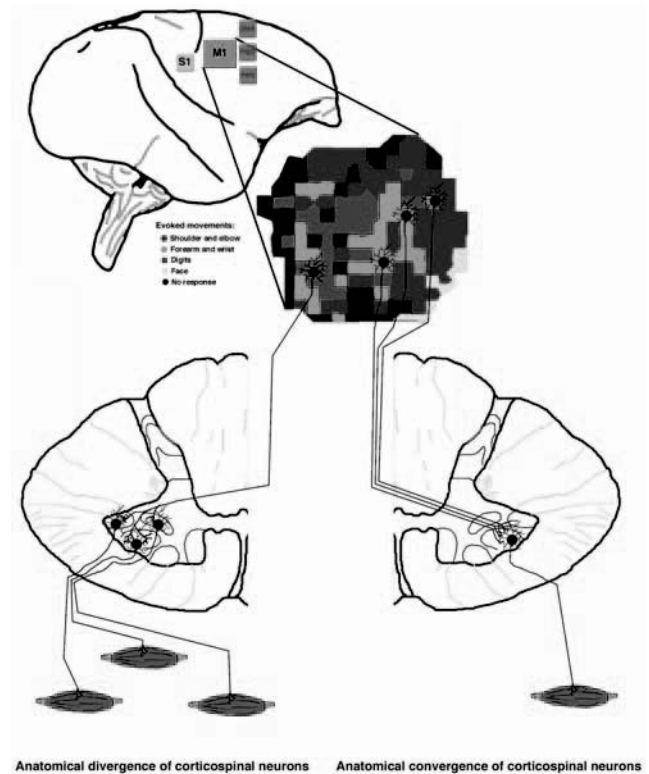


FIGURE 49-3

Anatomical divergence and convergence of corticospinal neurons. Upper: Example of a motor map of evoked movements in the primary motor cortex (M1) derived from intracortical microstimulation techniques. The map shows the intermingling of evoked digits (red), wrist and forearm (green) movements clustered in the middle of more proximal (elbow and shoulder; blue) movements. Lower left: Corticospinal divergence. One cell located in the digit representation of M1 projects to several motoneuronal pools in the spinal cord that, in turn, project to different arm muscles. This result has been demonstrated using both axonal tracing and spike-triggered averaging techniques (133, 134). Functionally, this illustrates that one very small area of the motor map can have a very widely distributed influence on the musculature of the arm. Lower right: Corticospinal convergence. Several cells located at various locations within the wrist and forearm representations in M1 all project to the same motoneuronal pool in the spinal cord, which then projects to a single muscle of the arm. This has been demonstrated using both intracortical microstimulation and stimulus-triggered averaging techniques (135, 136). Functionally, this illustrates that a wide surface area of the motor map can have a very focal influence on the musculature of the arm

use of visual guidance to compensate for deficits in somatosensory-motor integration (19).

The functional representation of the skeletal motor apparatus is represented in cortical motor areas in a topographic fashion, with the contralateral leg represented

more medially and the hand and face represented more laterally in M1. However, due to anatomical divergence of corticospinal neurons, a strict topography is not apparent when the spatial organization is examined on a more refined scale. It has been estimated that each corticomotoneuronal cell innervates about four or five separate motor neuron pools (20). Further, neurons originating corticomotoneuronal fibers innervating a single motor neuron pool are located in multiple sites within a topographic region in M1 (Figure 49-3). This anatomical divergence and convergence of corticospinal fibers, along with a dense network of local intracortical connections within M1 results in a substrate that provides a great deal of flexibility in its functional arrangement. In other words, it appears that motor cortex is expressly designed to allow for plastic reorganization of its local circuitry and ultimately, of its functional outputs.

### Use-Dependent and Skill-Dependent Modification of Motor Cortex Topography

A common technique for demonstrating the detailed topography of cortical motor areas in experimental animals is known as intracortical microstimulation (ICMS) (21). Based on ICMS results in non-human primates, the general topographic representation of specific body parts is quite consistent in M1, but substantial individual variability exists in the detailed topography on a more refined level, e.g., within the hand representation (Figure 49-4). The size of the hand representation can vary by over 100% in different monkeys, a difference that cannot be accounted for on the basis of the animal's size alone. It has been hypothesized that individual variation in motor maps is a result of each individual's sensorimotor experiences leading up to the motor mapping procedure (22).

The modifiability of the motor map has now been studied extensively in M1 of humans, non-human primates and rodents (caudal forelimb area) (23, 24). Soon after the learning of a new fine motor skill, the representations of the movements involved in the skilled task are enlarged. At least in experimental animals, specific combinations of movements used in the task emerge in ICMS maps (25). Presumably, local functional networks are established within the reorganized cortex, potentially reflecting the emergence of muscle and movement synergies within M1. Long-term potentiation of intracortical connections is likely to play a role in the emergent properties of reorganized cortex (26, 27). Plasticity in motor maps resulting from the acquisition of motor skills is both progressive and reversible.

Plasticity in motor cortex organization as a result of motor skill learning has also been shown in humans using fMRI techniques. While neuroimaging results represent a very different form of data, skill-dependent changes can be demonstrated during the acquisition of skilled motor

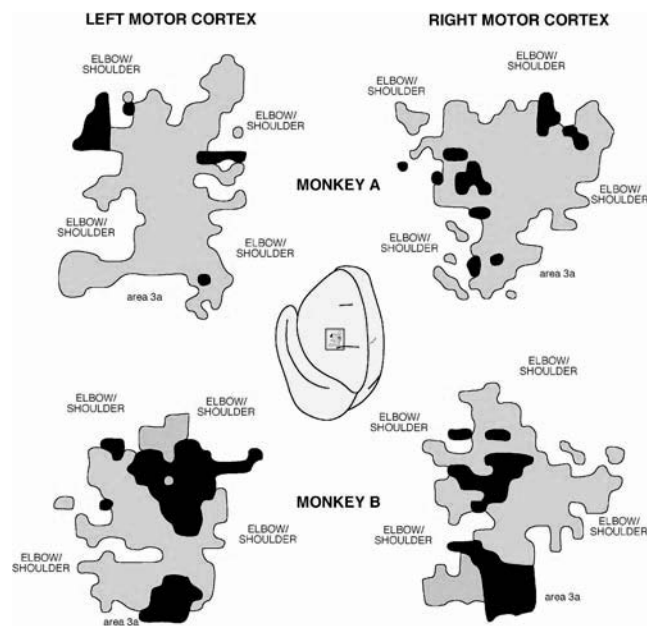


FIGURE 49-4

Individual variability in M1 maps in non-human primates. When the M1 maps of the hand representation are compared between hemispheres of the same animal, the mosaical patterns are similar on the two sides. For example, in both Monkeys A and B, the pattern of digit flexion representations (black) in the left motor cortex is roughly a mirror image of the pattern in the right motor cortex. However, when the digit flexion representation is compared between Monkeys A and B, the patterns are strikingly different, if not complementary. This high degree of individual variability in motor maps may result from the differential motor experiences of the animals prior to the mapping experiment. Graig denotes non-digit distal forelimb areas. Adapted from Ref. 22

tasks. However, the timing of the learning events may be critical to the particular changes that are observed (28). While the relationship between acquired skills and the size of motor representations holds for M1, the story may be more complex for other motor areas or for other motor tasks. For example, during the sequential learning of foot movements, cerebral blood flow was increased bilaterally in the dorsal premotor cortex and cerebellum during the execution of the movement. After a one-hour training session, blood flow in these regions was no longer increased during foot movement (29). As the authors suggest, these areas may be involved in cognitive strategies and motor routines to execute the foot movements, but are no longer involved once the sequence of movements is learned.

Structural changes in motor cortex also occur during the acquisition of motor skills. In rodents assigned to a skilled reaching task, reaching accuracy increased significantly at 3, 7 and 10 days of training. However, synaptogenesis (synapses per neuron) increased after 7 or 10 days of training, but not after 3 days of training. Motor map

plasticity occurred at 10 days of training only. Motor learning-dependent synaptogenesis is localized only to those motor regions undergoing the motor map changes (30) (Figure 49-5). Thus, structural and functional changes in motor cortex are co-localized, and are evident only in late stages of training, possibly related to the consolidation of motor skills rather than their initial acquisition (31). This late change in motor maps and motor cortex synaptogenesis is important in interpreting differences between fMRI results in human motor learning studies with electrophysiological and anatomical results in animal studies. The typical human studies are conducted over relatively short time intervals (minutes to hours), and thus, may be reflecting very different aspects of motor learning-dependent neuroplasticity.

From the standpoint of developing new rehabilitative interventions based on neuroplasticity principles, it is important to contrast the effects of skill learning with repetitive, but non-skilled motor activity (Figure 49-5). In

experimental animals, repetitive motor activity that does not induce improvements in motor skill or motor learning fail to alter motor map topography or synapse number (30, 32, 33) albeit induces angiogenesis (34, 35). This phenomenon has not yet been extensively studied, but may play a very important role in recovery at particular stages after brain injury.

### ACUTE AND CHRONIC CHANGES IN PERI-LESIONAL AND REMOTE REGIONS AFTER BRAIN INJURY

Following injury to the brain via trauma or stroke, a cascade of molecular and cellular events is set into motion in the surrounding tissue that results in both temporary and permanent changes in the anatomy and physiology of the affected structures (36). Many of these changes are pathological consequences of the injury (e.g., edema) and

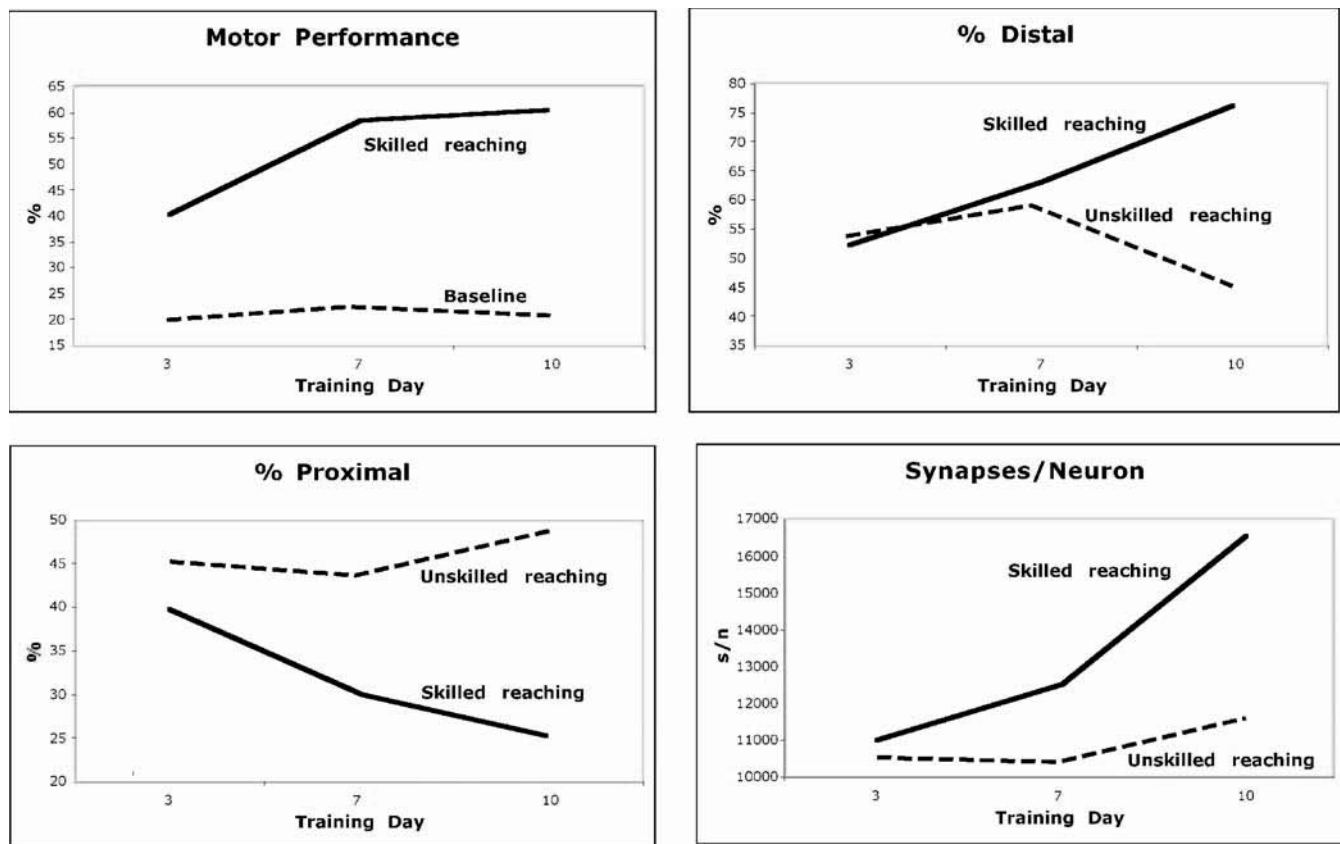


FIGURE 49-5

Functional and structural changes in motor cortex related to improvements in motor skill. As rats develop skill at a reach and retrieval task (upper left), distal representations occupy a progressively greater portion of the forelimb area (upper right), while proximal representations occupy a progressively smaller portion (lower left). In addition, synaptogenesis occurs during motor skill acquisition, especially during the later phases of motor learning (i.e., mostly at 10 days, but not substantially at 3 or 7 days; lower right). Simple repetitive tasks that do not require acquisition of new motor skills result in no neurophysiological map changes or synapse changes. Adapted from Ref. 31

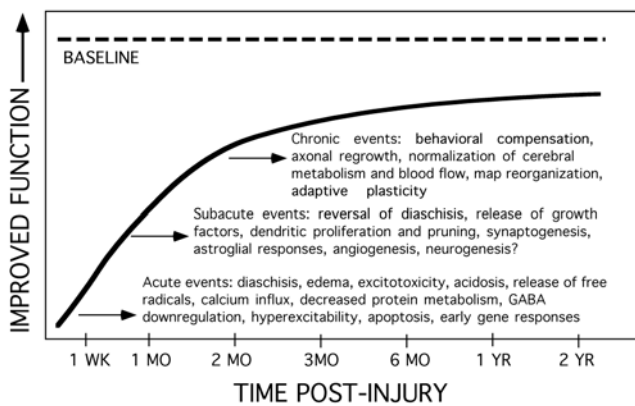


FIGURE 49-6

Cascade of acute, sub-acute and chronic events that are triggered by cortical injury. As acute pathogenesis subsides, improved sensorimotor function occurs. During the subacute phase, presumed restorative mechanisms are set in motion, such as dendritic arborization, release of growth factors and angiogenesis. Finally, functional and structural changes are consolidated in chronic phases as evidenced by alterations in axonal pathways and functional map configuration

have potentially damaging results. However, many adaptive processes may begin early in the post-injury stage and result in reduction of pathophysiological events or in neuroplastic changes leading to at least some restoration of function (37, 38) (Figure 49-6). While a thorough understanding of these processes at the molecular, cellular and network levels is just beginning, sufficient knowledge is now available to begin testing hypotheses about the effects of specific post-injury interventions on functional recovery and its underlying neuroanatomical and neurophysiological bases.

### Theories of Recovery

At least three general theories have been proposed to explain the substantial recovery that often follows brain injury, referred to here as reversal of diaschisis, compensation and adaptive plasticity (or vicariation of function) (Figure 49-6). As early as 1914, von Monokow discussed the role of diaschisis, or the temporary reduction in function of structures interconnected with an injured brain region, in the acute stages after injury (39). It is well known that both cerebral blood flow and metabolism are decreased in the region immediately adjacent to the injured tissue. Further, structures anatomically connected with the injured region undergo similar reductions in blood flow and metabolism. Gradually, blood flow and metabolism returns to the connected regions. Since this disruption is temporary, functional recovery is likely to be related, in part, to a gradual reduction in diaschisis.

Compensation in motor behavior is a common consequence of brain injury as the individual attempts to

supplant lost functions with alternative strategies. As an extreme example of compensatory behavior, a stroke survivor may begin to use the less-impaired limb for completing common tasks. However, more subtle changes in movement patterns occur even during use of the impaired limb. Stroke survivors with impaired function of the arm and hand may use proximal musculature in compensatory strategies to propel the limb forward (40). Depending upon the specificity of the motor endpoint that is assessed, such compensatory behavior could be missed, leading to the suggestion that motor performance has normalized. Even with the smallest experimental ischemic infarcts that can be made reliably in experimental monkeys, subtle changes in the kinematics of motor strategies take place, leading to the question of whether “true recovery”, i.e., return to normal, pre-lesion behavior, ever occurs (41). This is an extremely important, but often overlooked aspect of recovery that is critical for interpreting studies of neuroplasticity mechanisms after injury. Since use-dependent and learning-dependent changes are observable in the anatomy and physiology of normal, intact brains, it must be presumed that the development of compensatory motor patterns post-injury also alter brain structure and function.

A third general theory posits that functional recovery is largely dependent upon adaptive plasticity of intact, remaining brain structures. Various alternative terms have also been used to describe this theory, including “vicariation of function” and “neural compensation”. While this theory is also at least a century old, it has received considerable support in the past two decades from correlative studies in both experimental animals and in humans after brain injury. Underlying mechanisms thought to be involved in adaptive plasticity include unmasking of existing connections, long-term potentiation, long-term depression, axonal sprouting, dendritic sprouting, synaptogenesis and angiogenesis. Also, while the role of neurogenesis after brain injury is still controversial, some studies now suggest that brain injury can induce this process at least in some regions, and that neurogenesis may contribute to functional recovery (42).

### Neurophysiologic Alterations in Intact Structures After Brain Injury

Focal injury to the cerebral cortex does not simply result in a “hole” in the affected structure. Adjacent, intact cortical regions, as well as more remote cortical regions interconnected with the damaged area, undergo substantial physiological and anatomical changes. As early as 1950, Gles and Cole, using cortical surface stimulation techniques, demonstrated that if the motor representation of the thumb in primary motor cortex (M1) was destroyed in experimental monkeys, it reappeared in the adjacent, intact motor cortex (10). Later, it was demonstrated that a focal ischemic infarct in the primary somatosensory



cortex that eliminated the sensory representation of a single digit resulted in the eventual re-emergence of the digit representation in the adjacent tissue (43). These results would seem to support the adaptive plasticity or vicariation hypothesis. However, when newer intracortical microstimulation (ICMS) techniques were applied to M1, the vicariation phenomenon could not be replicated (25). Instead, when small, focal infarcts were made in the digit representation of M1, a further loss in digit representation occurred in the adjacent M1. While it may be tempting to dismiss the earlier results of Glee and Cole based on the spatially crude surface mapping techniques that were used, another important factor was found to contribute to the findings. This factor – the post-injury motor experience of the animal – has great impact on the ultimate, chronic condition of the motor map, and, very likely on the ultimate motor performance that can be achieved.

To determine the effects of post-injury experience on reorganization of motor maps, Nudo and colleagues encouraged the use of the impaired limb by placing a restrictive jacket on experimental monkeys. The jacket contained a long sleeve that extended the length of the less-impaired forelimb, and ended in a soft mesh mitt on the hand. The restricted hand could still be used for climbing, but was ineffective for grasping small objects, a task that was difficult to perform with the affected hand. Beginning about five days post-injury, two half-hour sessions of reach/grasp training were conducted each day. Several days to weeks were required to retrain skilled use of the affected hand, but eventually motor performance on the experimental task was similar to pre-lesion levels. Following this recovery period, the ICMS-derived motor maps revealed that the digit representations in the intact areas were maintained. In some cases, they expanded into regions where prior mapping revealed proximal representations (44). Thus, motor experience after injury can drastically alter the ultimate functional organization of motor cortex (Figure 49-7).

This phenomenon is not limited to the adjacent cortex. In other non-human primate experiments employing slightly larger lesions encompassing the entire M1 hand area, hand representations in the premotor cortex were enlarged several months later, even in the absence of post-injury training. Further, the magnitude of the premotor enlargement was directly related to the size of the injury in M1 (45) (Figure 49-7). Since premotor cortex has reciprocal connections with M1, it is not surprising that this region is altered. But the enlarged representation related to the size of the M1 injury suggests that it may play a significant vicarious role in recovery.

### Anatomical Alterations in Intact Cortical Structures After Brain Injury

In concert with behavioral recovery and neurophysiological remodeling, injured brains undergo significant

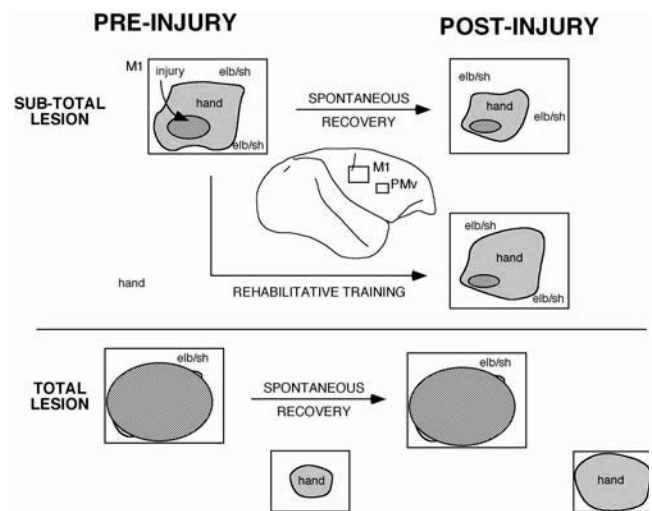


FIGURE 49-7

Functional alteration of local and distant cortical organization following focal injury. Sub-total lesion: If the injury is small enough, reorganization is primarily confined to the local adjacent tissue. For example, a subtotal injury to the M1 hand area results in changes in representational maps in the spared hand area adjacent to the injury. Post-injury rehabilitative training can have a profound influence on the inevitable map configuration. Total lesion: After a total lesion of the M1 hand area, other motor regions interconnected with M1 are stimulated to reorganize. For example, the hand representation in the ventral premotor cortex (PMV) enlarges. This premotor area normally has reciprocal connections with the injured M1. Adapted from (45)

anatomical plasticity in neuronal and non-neuronal structures. In rat motor cortex, intracortical fibers in the bordering intact tissue display orientations different from those seen in normal animals, suggesting that injury induces local axonal sprouting (46). Arteriolar collateral growth and new capillaries also form in the ischemic border (47). Significant neuroanatomical changes also occur in the contralesional (intact) motor cortex, but the role of this cortex in functional recovery of the affected limb is still a subject of debate. Recent results from animal studies suggest that the neuroanatomical changes in the intact cortex occur as a use-dependent or skill-dependent change due to increased use of the less-affected limb (48).

The latent potential for enhancing neuroanatomical plasticity mechanisms after stroke has been demonstrated by the use of mutant mouse strains that lack the Nogo receptor. Nogo is a protein involved in the inhibition of axonal growth. Mice lacking the Nogo receptor recover motor function after stroke better than controls. Further, rats subjected to anti-Nogo antibody treatment initiated one week after stroke resulted in better behavioral recovery compared with controls. Further, sprouting

of contralateral corticorubral and ipsilateral corticospinal fibers was observed (49). Pharmacologic treatment with D-amphetamine after stroke has also been shown to enhance neocortical sprouting, synaptogenesis and behavioral recovery after stroke (50).

### **PHYSIOTHERAPEUTIC TREATMENT FOR MOTOR DISABILITY AFTER BRAIN INJURY: CURRENT PRACTICE**

Since it is now clear that certain types of behavioral and pharmacologic interventions have the potential to alter neurophysiological activity and neuroanatomical structure, it may be helpful to examine the various therapeutic approaches used in post-injury rehabilitation, and consider their potential for maximization of recovery based on neuroplasticity principles. This discussion may lead to a better understanding of the underlying mechanisms of rehabilitative therapy by pointing out the current gaps in our basic knowledge. It also may help us to refine therapeutic interventions to take advantage of the modulatory role that specific behavioral and pharmacological therapies play.

#### **The Maximization of Motor Recovery Through Diverse Approaches**

Treatment of upper limb impairments following brain injury (such as that occurring after stroke) follows either: 1) principles of neurofacilitation or 2) principles of functional retraining. Traditionally, the choice between these rehabilitation strategies has been based on the phase of stroke recovery. Whereas in the acute/subacute phase, therapy typically focuses on the prevention of maladaptive compensatory strategies while promoting the recovery of normal function, in the chronic phase, the emphasis is placed on maximizing function, often through the teaching of compensatory strategies (51).

*Principles of Neurofacilitative Approaches* Neurofacilitative approaches, such as Rood, Brunnstrom, Bobath, Proprioceptive Neuromuscular Facilitation (PNF) and Sensory Integration (SI) therapy, are usually used in early post-injury stages to favor motor recovery following a stroke, when most of the recovery seems to occur (52). These approaches focus on the recovery of normal movement. Unwanted movements and spasticity are inhibited and normal patterns are facilitated under the assumption that regaining of voluntary control over key movements will transfer to functional improvement. These approaches are based on empirical assumptions that motor impairments are a consequence of a disruption of central nervous system (CNS) hierarchical and reflex motor control

(53–57). In the traditional view of these approaches, recovery of motor function follows the same chronology that is observed in neurodevelopmental stages, supposedly reflecting the CNS efforts to reestablish its internal hierarchical order that was disrupted by the neuronal loss consequent to the injury. Therefore, these approaches utilize neurophysiological phenomena (e.g. reflex pathways) to favor ‘normal’ motor behaviors and are largely based on neurodevelopmental knowledge (58). Whereas largely used and trusted by therapists (59, 60), in general they have not resulted in substantial impact on patients’ recovery when examined in controlled trials (61–64) and seem to result in similar behavioral outcomes when compared to each other (65–67).

Currently, to our knowledge no studies have explored physiological or morphological effects of neurofacilitative approaches on the CNS. This contrasts with the large number of mechanistic studies that are related to approaches based on movement repetition and retraining. However, it should be noted that the current absence of basic research investigating the effects of these approaches may be due to technical challenges rather than a weaker scientific rationale. Among the technical difficulties, because the NDT approach is specifically adapted for the individual’s particular needs and because it involves a high level of therapist manual expertise, inter-subject and inter-therapist variability is very high, making it quite difficult to standardize protocols. Hopefully, in the near future, the mechanisms of action of these approaches will be investigated. Currently, the urge for experimental support for the widely used clinical practice is felt and underlined by the NDT community (68). The desire to provide an evidence-based practice is supported by the Neuro-Developmental Treatment Association, which is currently providing financial support for research and favoring the development of a consistent knowledge base among therapists.

*Principles of Functional Retraining* Recently, studies evaluating the mechanisms underlying motor acquisition and motor control have resulted in the elaboration of behavioral treatment approaches based on practice (51, 69, 70). In these approaches, it is believed that the hemiparetic subject has distorted central motor programs resulting from CNS cell death. Based on the assumption that repetition of movements has the same effects as the ones reported for normal individuals (71), it is believed that practice establishes novel motor plans for the resolution of encountered motor problems (72). Additionally, it is taught that movement repetition improves behavior by affecting muscle weakness, an important problem affecting upper limb function (73–75).

Initial evaluations of the efficacy of repetition of movement, in order to improve motor outcomes following stroke, have provided encouraging results. Several studies have shown that repetitive, concentrated practice

improves motor outcomes (14, 76–80). Additionally, diverse practice approaches have been explored in order to maximize retention and transferability (81–88). At this point, whereas it is well established that practice improves motor outcomes and function following stroke, currently a consensus on a precise and consistent protocol to use to maximize the recovery is far from established. The elaboration of standardized training protocols based on principles of motor learning, retention and transferability specific to the hemiparetic population, is one of the most urgent needs for patient management.

While animal models have frequently been used to optimize basic therapeutic strategies in preclinical drug trials, their utility has been under-appreciated. Surely, animal research allows investigation of mechanisms through which practice favors recovery and the identification of morphological and physiological processes that accompany improved motor performances. Whereas physiological changes at the level of the motor cortex induced by practice following stroke has been shown (44), the impact of diverse types of practice, intensity or even the time at which practice is most beneficial for the modulation of adaptive physiological and or morphological changes has yet to be investigated. For example, it was recently shown that rats undergoing training consisting of repetitive movements demonstrated functional and structural plasticity within the same cortical regions (30). This study provides strong evidence that synapse formation and physiological expansion of cortical representation of movement are concomitant and probably inter-dependent adaptive processes playing important roles in learning. Knowing that learning and practice are so influential in the recovery from stroke, the investigation of the parallel changes of dendritic arbors and physiological reorganization of motor maps in M1 or in premotor cortex will be of great interest. In the near future, the choice of treatment, intensity and schedule of therapy at different stages of stroke (e.g. acute, chronic) could be directed to take advantage of the most prolific stages of morphological and physiological reorganization.

Although it is a long held belief that most of the rehabilitation of stroke patients occurs in the first few weeks to months following stroke (Duncan and Lai, 1997), there is little evidence available indicating that physical rehabilitation is effective for patients with chronic CVA, and the literature is even equivocal on the value of physical rehabilitation for sub-acute patients (89, 90). However, the fact that some patients with a given extent and locus of lesion recover more movement than others suggests that additional factors may be involved. Taub and colleagues suggested that some motor abilities were possible, but were not reinforced. In the vernacular of classical conditioning, these behaviors were extinguished or actively inhibited (89). From this assumption, it was

stipulated that function could be improved in chronic stroke patients. In particular, this group has developed an innovative approach known as constraint-induced movement therapy (CIT) that has received a great deal of attention in the last decade. The idea behind the application of CIT originates from fundamental experiments conducted in non-human primates following peripheral deafferentation (91). In these experiments, disuse of the affected upper limb of non-human primates was observed following the injury. This maladaptive behavior persisted if no manipulation was introduced, even after a three to six month spontaneous recovery period. At that point, the function of the deafferented limb could be greatly enhanced by forcing its use by restraining the non-affected limb (92). This led to the ‘learned non-use’ hypothesis which stipulates that non-use, or less than maximal use, of the deafferented limb results from negatively reinforced attempts to use the affected limb. This negative feedback would consist of unsuccessful behavioral consequences of attempts to use the affected upper limb (e.g., absence of reward for goal-directed activity, or painful execution). After the initial recovery period, when the ability to use the affected limb is stable, behavioral sequelae caused by the learned non-use remain. Therefore, because of the phenomenon, the actual use of the affected limb is much less than its true potential (89, 93, 94). Strong support for the learned non-use formulation came from a study where restraint was applied directly following the deafferentation of the upper limb of an animal for a 3-month duration, therefore preventing the learned non-use phenomenon to occur (95). When the restraint was removed, the animals used their deafferented limb. Also, when deafferented prenatally, animals exhibited purposive use of the deafferented limb from the first day of extrauterine life (96, 97). In that experimental paradigm, the use of the upper limb following the lesion was also restricted because of the limited intrauterine space, thus preventing the negative feedback from unsuccessful usage of the limb and supposedly the learned non-use phenomenon from developing.

Physiologically, it can be assumed that deafferentation is a lesion which, like potentially many others, such as traumatic brain injury or stroke, creates a disruption of sensorimotor integration loops (98–100). By this logic, disruption would result in initial poor motor behavior. The progressive reestablishment of sensorimotor integration loops through motor behavior favoring CNS adaptive mechanisms may underlie a substantial amount of spontaneous recovery from these lesions. However, during the adaptive period, the learned non-use phenomenon would negatively intervene, making the subjects subconsciously or consciously learn that the use of the affected limb results in poor behavioral outcomes. The negative feedback from these outcomes would reinforce preferential usage of the non-affected limb. In that view,

the learned non-use phenomenon would not only be present following deafferentation, but also following any injury disrupting sensorimotor integration loops. Therefore, the application of a restraint on the unaffected limb, to force the use of the affected limb, should result in improvement of motor outcomes in numerous neurologic, and even orthopedic, conditions (101).

In the original application of the learned non-use hypothesis to the hemiparetic population, a simple arm-restraint was employed (102). In that study, stroke and head-injured patients were required to keep their uninjured upper extremities within a hand-enclosed sling during waking hours over a two-week interval. Functional improvements in diverse tasks and in force were reported, and most of them were maintained when examined in a one-year follow-up assessment. The results supported the hypothesis that learned non-use occurs in select neurological patients and that this maladaptive behavior can be reversed through application of a forced-use paradigm. In a second experiment (103), use of the sling for 14 days was combined with six hours of practice of functional movements with the impaired limb for 10 of those days. The behavioral training paradigm consisted of operant conditioning (104). Patients demonstrated improvements beyond what had been reported with the sole use of the sling, and improvements in motor performance were maintained during a two-year period of follow-up. The increase of motor improvements obtained from the combination of behavioral training with the wearing of the sling is a strong indication that, in addition to reversal of learned non-use, additional factors may be involved in the recovery in chronic stroke patients<sup>1</sup>.

Positive results using the CIT paradigm have been reported in several experiments (94, 105, 106) and by unrelated research groups (107, 108), repeatedly demonstrating large effect sizes for the Motor Activity Log (MAL) and for the Wolf Motor Function Test (WMFT). In addition, more recent studies using a modified CIT demonstrate that upper extremity function can be improved after TBI. Most importantly, improvement in motor skill made by the patients has been shown to be transferable to other activities in their daily lives. It should be pointed out that the constraint increases the time of treatment to up to 90% of waking hours of the subject. Thus, it imposes a discipline that might otherwise be difficult to achieve in practice. It can be argued that it probably is the simplest and most reliable way to reach such a high level of intensity for a clinical intervention. In the absence of constraint, if a task introduces too many obstacles to execute with the affected limb, the subject will naturally have the tendency perform it with the other limb, therefore limiting the learning

experience with the impaired limb. The constraint forces the patient to immediately apply the motor skills he is learning during daily treatment in a natural and very significant location: at home. Learning is context-dependent, meaning that an important factor in the retention of motor skills is the relationship between the context of practice and the context of application (109). Therefore, the level of intensity of intervention and direct context-dependent application of the learned motor patterns during the day might explain why the therapy has such a high impact on the performance level on tests evaluating functional motor state of the patient (e.g. MAL; WMFT).

The paradigm used in non-human primate experiments is strikingly similar to CIT. Monkeys wore a jacket with a long sleeve restricting fine control by the less affected limb. Thus, these animal experiments may be very useful for evaluating various aspects of the CIT protocol (e.g., timing, intensity, specific behavioral factors, etc.). From the monkey studies, it would appear that the repetitive behavior is the more important factor in CIT, rather than the presence of the constraint device. Recovery of hand representations in primary motor cortex is very rapid when the use of the restraint jacket is combined with repetitive training. However, when the restraint device is the sole source of motivation to use the impaired limb, normalization of motor maps occurs extremely slowly, if at all. Monkeys that wore a restraint jacket for up to one year did not display as much map recovery as monkeys engaged in repetitive training for only two weeks (110).

A series of experiments to evaluate the presence of cortical representation changes, paralleling the behavioral changes resulting from CIT, has also been performed (91, 111, 112). These studies reported increased cortical representation areas of the affected arm following treatment, an upper limb representational map size that was similar in both affected and less-affected hemispheres at a 6 months follow up, and shifts of the center of the output map, suggesting recruitment of adjacent brain areas examination. This last result has been related by the authors to the phenomenon that has been reported in monkeys undergoing repetition of movement therapy following a cortical ischemic lesion (44). Therefore, human studies now support the hypothesis that CIT modulates recovery through processes that are similar to the ones that are known to occur following motor learning through practice and repetition.

As previously mentioned, one of the interesting results that came from these studies was that, in addition to the reversal of the learned non-use phenomena, other factors appeared to be involved in the motor recovery of chronic stroke subjects. In fact, it was even shown that subjects that were undergoing intensive physical therapy, consisting of aquatic therapy, neurophysiological facilitation,

<sup>1</sup>Discussion of this particular topic can be found below.

and task practice showed a level of improvement similar to that of sling restraint of the less-affected arm, combined with intensive task practice or shaping (94, 105). However, in these experiments, the intensive therapy control groups showed higher levels of decrement of arm use at the two year follow up in comparison to the CIT group. Therefore, it appears that one of the advantages of the usage of a sling is the higher retention of use of the affected limb at the two-year follow-up, and that the common factor in all techniques producing an equivalently large treatment effect is repeated use of the more-affected upper extremity (89). It thus can be suggested that chronic hemiparetic patients have the capacity for functional motor learning and that they have not maximized their motor potential after traditional acute care.

In conclusion, we would tend to consolidate the preceding literature into one treatment hypothesis: Intensive treatment based on repetition creates plastic changes that are associated with learning (which might include reversal of learned nonuse). This probably acts through positive behavioral conditioning of the use of the impaired limb resulting in learning and amelioration of the general motor schema of the upper limb.

### **Too Much, Too Early?**

After injury to the sensorimotor cortex in rats, extreme use of the affected limb can result in an enlargement of the lesion and further motor impairment (113). If the unimpaired limb is placed in a restrictive cast after cortical injury, rats must rely heavily on the impaired limb for posture and locomotion. Forced overuse of the impaired limb during the first week after injury results in expansion of the injury and poorer motor performance (114). Forced overuse during the next seven days does not result in injury expansion, but nonetheless resulted in poorer motor performance. More recently, it has been shown that after TBI in rats, neuroplasticity-related intracellular signaling proteins are disrupted if voluntary exercise is provided within the first week post-injury (115). These studies strongly suggest that there are specific vulnerable periods for maladaptive effects of use after injury. Timing of these maladaptive effects must be considered along with timing of adaptive effects in any rational therapeutic design for treatment of motor deficits after injury.

### **Assessment of Efficacy**

The assessment of efficacy of clinical approaches is an important issue, not only for stroke and brain injury recovery, but for the entire field of neurorehabilitation in general. Particularly in the cases of stroke recovery, one important question surrounding this topic is: Should we focus on the return of “normal” movement (true recovery) or just on return of function at any cost (i.e., compensatory

strategies)? This question extends beyond the clinical field and is also debated in the literature discussing animal models of stroke (40, 41, 116). It also raises the question of evaluative tools. Obviously, very different tools are needed to evaluate the divergence from ‘normality’ of movement and functional capacities of a patient. Whereas evaluation tools focusing on the ‘abnormalities’ of movements are much more useful and appropriate to the practice of neurodevelopmental approaches, newer, strictly functional scales are used in several research protocols to measure the impact of movement repetition based treatments. Particularly, in the cases of CIT, the validity of the clinical tests they traditionally use to assess motor recovery has been questioned (106, 117, 118). These tests only evaluate function and use, and do not evaluate the use of compensatory strategies. In fact, the treatment effects become much more uncertain when using evaluation tools monitored by trained therapists, such as the Fugl-Meyer (119) or the Barthel index (118). It can be argued that the WMFT and MAL are self-reports that could circumvent the blinding process (118); familiarizing patients with the MAL questions on a daily basis may permit recollection of previous responses, thereby narrowing the choice points on the MAL. This effectively reduces the variability, and enhances the effect size (119). On the other hand, it can also be argued that the ultimate goal of therapy, specifically at a chronic stage, is to improve function and use of the affected limb and that the WMFT and MAL are specifically designed and were shown to do this well (117). Alternatively, for the validation and evaluation of learning processes, movement kinematics could be assessed. A recent study showed that in chronic patients, when immobilizing the trunk, the subjects use their shoulder and elbow joints in a more normal way (120). The use of the trunk helps patients to create end-point trajectories that are more similar to healthy subjects. This study underlines that compensatory behavior can potentially be detrimental to maximization of function, in this case, limiting the range of reaching. Whereas maximization of function is the goal of rehabilitative approaches, the identification of these detrimental compensatory strategies is necessary to achieve this goal. Novel evaluation scales are being developed (121) and will hopefully help clinicians in that task.

### **Treatment Groups and Valid Controls**

It now seems obvious that the evaluation of treatment outcomes must take into consideration the type of treatment and the initial level of function of the targeted population (52, 122). Intrinsic, non-treatment-related elements are key determinants in the level of potential benefits a patient derives from a particular treatment. Whereas the initial level of function (as reflected by clinical assessments such as the Fugl-Meyer) has traditionally

been used as the main predictor for recovery, other factors are now identified as better predictors. The initial grade of paresis appears to be the most important clinical predictor for motor recovery (123). Additionally, motor evoked potentials (MEP) seem to be highly predictive for the occurrence of motor recovery (124–126). It was shown to be a much better predictor than clinical examination, infarct size and location, age, gender, and stroke type (infarction versus hemorrhage). Also, preservation of the corticospinal tract with MRI imaging was also found to correlate with good recovery, confirming the TMS studies (127). This confirms that studies evaluating the efficacy of different clinical approaches need to have stringent selection criteria for their subjects. Recovery from strokes can vary largely between individuals. For example, purely cortical stroke survivors recover better than purely subcortical or mixed cortical-subcortical strokes. Decreases in the level of recovery can be observed from cortex, corona radiata, and posterior limb of internal capsule (128). This suggests that recovery of upper limb movement is heavily dependent on the preservation of corticofugal fibers (128, 129). Also, the recovery period is approximately twice as long for patients with severe paresis (15wk), compared to patients with mild paresis (6.5wk) (130). Therefore, to truly evaluate the impact of a treatment on stroke survivors, studies should be designed to include patients with similar predicted outcomes in each experimental group. Additionally, if some subjects have intrinsic conditions rendering them unable to benefit from a certain approach, they should be studied separately to identify the substrate of this failure and the potential alternative approaches from which they could benefit more. For example, a preliminary study to investigate the integrity of short-term motor memory in stroke subjects indicated that patients with low Fugl-Meyer and executive function scores had problems modifying their motor commands based on previous experience (131). Such results raise important questions concerning the use of movement repetition in this particular population of hemiparetic patients.

### SUMMARY

Our understanding of recovery from damage to the central nervous system has evolved tremendously in the last few decades. Fundamental research on the diverse physiological, morphological, molecular and genetic changes resulting from ischemic damage and the association of certain phenomena to behavioral recovery has drastically impacted stroke management. Evolving knowledge of plastic changes accompanying functional recovery coming from both animal studies and technological advancements in humans (e.g., fMRI) might create a entire new set of outcome predictors and or surrogate markers of

recovery states useful for both study design and patient treatment choices. These novel indicators might also direct the type, intensity and duration of treatments. For example, cortical representation of body segments evaluated with TMS could become a means to identify the endpoint for treatment. When patients demonstrate a plateau in physiological reorganization, this could imply that most of the adaptive changes have already taken place. Whereas much work has been done, obviously, many questions are still unanswered. Most of the experiments that have been performed so far have included only subjects showing high functional scores. Unfortunately, a large proportion of hemiparetic stroke patients show mild improvements with currently available treatments. Surely, significant work in both animals and humans needs to be accomplished to better understand and provide more efficient treatments to individuals with brain injury.

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# 50

## Therapy Interventions for Mobility Impairments and Motor Skill Acquisition After TBI

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**I**nnovations in mobility rehabilitation after brain injury derive from recent advances in neuroplasticity and neurorecovery. In particular, our understanding of motor recovery after brain injury is being influenced by basic science work that demonstrates that the process of motor skill acquisition is essential to promote both behavioral changes in motor performance and morphologic changes in neural structures within the motor cortex. (Please refer to Chapter by Nudo & Dancause for discussion of neuroplasticity and effects on brain injury recovery). The complexities of rehabilitation after brain injury comes from the usual situation that both neural structures that interfere with normal movement (i.e., corticospinal neurons and their connections) as well as those that impact the cognitive processes associated with motor learning are affected. Therefore, physical neurorehabilitation needs to include intervention strategies that address impairment level motor deficits that result after brain injury such as weakness, abnormal movement synergies, and abnormal tone as well as the intrinsic and extrinsic factors that promote motor learning and the acquisition of motor skills needed to increase function.

The field of neurorehabilitation needs to experience a paradigm shift. Advances in basic science research provide important understanding of the physiologic events that occur after brain injury and the neural processes that modify and impact recovery. The challenge

for neurorehabilitation specialists who work with individuals with brain damage is to incorporate the strategies that are elucidated by the animal studies and ultimately design the clinical trial studies that will systematically examine these treatment paradigms within the clinical setting. Unfortunately, clinical trials that specifically examine treatment efficacy in human populations with traumatic brain injury (TBI) are sparse. However, evidence from the work done in individuals with stroke-related brain damage may provide a basis for the design of future TBI trials.

The intent of this chapter is to focus on rehabilitation approaches that address motor recovery; specifically, primary and secondary impairments that affect mobility and the process of motor skill acquisition after brain damage. This chapter will discuss factors that affect motor skill acquisition after brain injury, review traditional treatment approaches that address physical impairments that affect mobility, and present some examples of innovations in therapeutic interventions that address the acquisition of skills and promotion of meaningful functional recovery.

### **DISABLEMENT MODEL**

Recovery from brain damage is multi-factorial and involves more than just the recovery and reorganization of neural structures. Contextual factors such as environmental

influences like physical barriers, social support system and access to funds and services or personal factors such as age, gender, health status and personal lifestyle behaviors are all powerful predictors of outcome after TBI. For this reason, it is helpful to use an organizing framework such as the International Classification of Functioning, Disabilities, and Health (ICF) disablement model when approaching problem identification, goal formulation, and treatment planning. Additionally, the multiple dimensions of this model reflects the need for an interdisciplinary team to adequately address all of the contributing factors to disability after TBI.

The ICF disablement model is a classification system developed and disseminated by the World Health Organization (WHO) (1). The ICF characterizes the impact of a condition such as TBI according to the following dimensions: body function and structures, activities, and participation.

- *Loss of body functions and structures* include the impairments that result as a primary or secondary consequence of the brain injury. The neuromuscular motor impairments that will be discussed in this chapter include such things as impairments in voluntary movement, balance and postural control, and abnormal tone that result from direct insult to brain structures. Secondary impairments are the musculoskeletal conditions that result from immobility or excessive muscle tone such as muscle contractures, restricted joint mobility, and disuse weakness and deconditioning.
- *Activities* are the tasks that the individual performs such as walking, feeding, dressing, and other self-care related functions. Activity limitations reflect the difficulty that the person has in functional task performance.
- *Participation* reflects the individual's involvement in life and societal activity. There are 9 participation domains that include: personal maintenance, mobility, exchange of information, social relationships, home life and assistance to others, education, work and employment, economic life, and community, social, and civic life. The focus of this chapter will be therapeutic approaches associated with improving participation in mobility related tasks and activities.

Disablement models are a meaningful way to determine and evaluate the consequences of disease or injury. The original intent of the ICF classification (and its predecessor the ICIDH-2) was to evaluate the process of health care delivery, which required the need to develop and measure outcomes at each level of the disablement process (2). Because of this, recent trends in rehabilitation literature (particularly in randomized clinical trials that examine the efficacy and effectiveness of rehabilitation interventions)

include levels of measurement that reflect outcomes at the impairment, activity, and participation levels.

Another application of the disablement schema is to provide an organizing framework for rehabilitation intervention such that rehabilitation approaches could be developed and standardized in order to identify goals that are aimed to address problems at the levels of impairment, activity, or participation. Designed to assess the consequences of disease or injury, the disablement classification system has an implicit assumption that interventions that improve impairments will lead to improvements in functional limitations, and hence, reduce disability. Quinn and Gordon (3) propose that one of the limitations of using the disablement model as a framework for intervention is that it takes a reductionist approach to rehabilitation. A reductionist approach would emphasize that disease or injury leads to disablement; therefore, reduction of disease or injury-related impairments would be the focus of rehabilitation. In contrast, they suggest that the process of rehabilitation is the reverse, such that, rehabilitation interventions are designed to lead to recovery (Figure 50-1). A physical rehabilitation approach that emphasizes recovery would 1) identify the roles related to self-care, social and recreational pursuits, and occupation that an individual desires to assume or reassume after injury, 2) identify the skills required to successfully achieve these pursuits, 3) determine the physical limitations and cognitive processes that are impaired and contribute to the functional deficits, and 4) design interventions that address physiologic mechanisms of recovery at both the impairment and skill levels.

Recent advances in neuroplasticity provide mechanistic validation to a rehabilitation approach that emphasizes

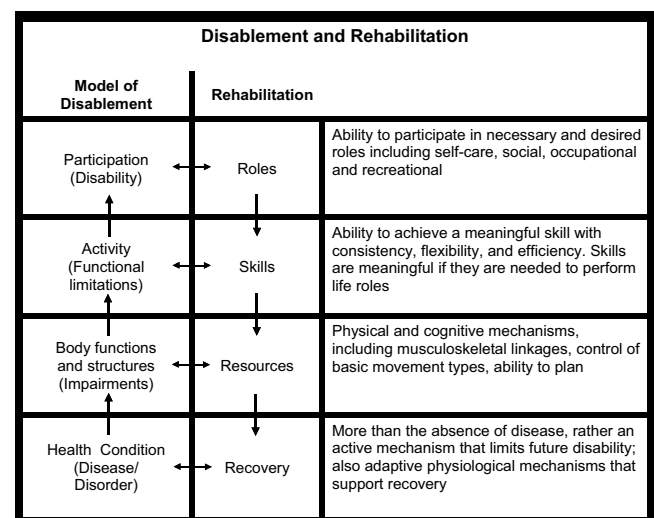


FIGURE 50-1

Conceptual framework of functioning and health in rehabilitation. Adapted from Quinn and Gordon (79)

recovery and skill acquisition. Consistently, animal models of recovery after brain damage demonstrate that the process of motor skill acquisition is a critical component that subserves both functional and neurological recovery (4–11). One of the major premises of a paradigm shift in physical rehabilitation of individual’s with brain injury is the need to design therapeutic interventions that promote the acquisition of motor skill as well as address the direct and indirect impairments that occur to the neuromuscular system.

**PRINCIPLES OF FUNCTIONAL TRAINING AND MOTOR SKILL ACQUISITION**

The recent advances in neuroplasticity discussed by Nudo and Dancause in Chapter 49 of this book provide substantial evidence for the neurophysiologic and neuroanatomic mechanisms that underlie the process of motor skill acquisition and the importance of skill acquisition in recovery after brain damage. Clinicians in the neurorehabilitation field need to develop strategies to integrate the concepts

of neuroplasticity and motor recovery with the clinical environment where the learning of motor skills occurs. Figure 50-2 proposes a Theoretical Model for Neurologic Therapeutic Intervention that incorporates our current understanding of neuroplasticity and neurorecovery. This model is based on the assumption that neuroplasticity is driven by the acquisition of motor skills. What are the therapeutic principles that should be incorporated into therapy sessions in order to optimize the learning experience and maximize the level of skill acquisition for our patients? Recent research in neurorehabilitation suggests that key principles of motor skill acquisition and learning and principles of exercise can be applied to increase neurorehabilitation effectiveness and include the importance of practice and feedback, task-specificity, and training intensity. These principles provide important guidelines for the design and delivery of therapeutic interventions. Another important aspect of the neurotherapeutic model is at the level of assessment, whereby, the therapist analyzes functional task performance and determines the primary and secondary impairments that contribute to functional deficits. The organization of this chapter is to elucidate each of the critical factors that guide the clinician in the design of therapeutic programs that drive neuroplasticity through the process of skill acquisition. In addition, this chapter discusses the mechanisms and intervention strategies of the primary and secondary impairments of the neuromuscular and musculoskeletal systems that most commonly affect mobility after TBI.

**Process of Motor Skill Acquisition After Brain Injury**

Motor skill acquisition is the process by which an individual learns a motor skill. As with other cognitive processes such as language, verbal learning or declarative memory, motor learning occurs within various regions of the cortical and subcortical structures that are involved in the formation of a motor program that is parameterized in time and space to accurately meet a task goal. For example, a child learning to hit a baseball has to develop the strength and coordination to swing a bat with the speed and accuracy to meet the ball as it passes over the plate. The development of the sensorimotor representation of an action plan occurs in cortical sensorimotor structures such as the primary and secondary motor and sensory cortices. However, the initiation and retention of an action plan occurs in prefrontal, basal ganglia, and cerebellar structures. Therefore, motor skill acquisition and retention occurs throughout a neural network that involves all of these movement-related cortical and subcortical areas (12–14). Obviously, the impact of TBI on motor skill acquisition is profound since individual’s post-TBI can have involvement with structures that directly impact force production (i.e., motor cortex and direct connections to

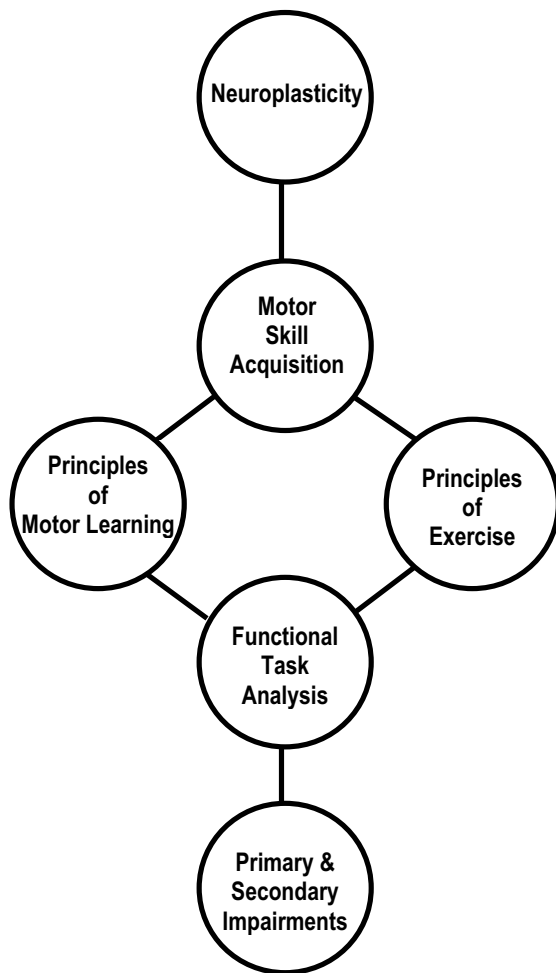


FIGURE 50-2

Theoretical model for neurologic therapeutic intervention

corticospinal tract of spinal cord) and coordination (i.e., cerebellum and basal ganglia effects on motor control) as well as with other cortical and subcortical areas associated with action plan development, initiation, and retention.

When working on motor skill learning with individuals with TBI, it is particularly important to appreciate the distinction between declarative (explicit) and non-declarative memory (implicit) systems since it is common that patients will present with cognitive deficits which interfere with their ability to have declarative recall but may not interfere with their ability to learn motor skills. The explicit and implicit learning systems are functionally and neuroanatomically distinct (15, 16). Declarative memory is memory for facts and events and is mediated by the medial temporal areas that include the hippocampus and diencephalic nuclei. Patients' post-TBI who are in the period of post-traumatic amnesia have declarative memory deficits as a result of damage in this neural system. In contrast, implicit or non-declarative memory is a collection of abilities that includes the formation of skills and habits, priming and perceptual learning, classical conditioning, and nonassociative learning. The implicit learning systems are not dependent upon the medial temporal areas that support declarative learning. Motor skill learning is a form of implicit learning in which changes in motor performance with practice can occur without conscious awareness of all of the movement-related abilities that are being learned. The areas associated with implicit learning are those that participated in the original learning; therefore, the sensorimotor, prefrontal, basal ganglia, and cerebellar areas, which comprise the neural network for movement, are the areas that are most likely to subserve the implicit motor skill learning system.

The dissociation between declarative awareness and skill learning has been demonstrated in healthy individuals (17) as well as those with brain damage due to Alzheimer's disease (18, 19), Parkinson's disease (20, 21), encephalitis and anoxia (22), and TBI (23, 24). Clinically, this dissociation is significant since it reveals that there is not a direct relationship between the ability to learn new declarative information and the ability to learn motor skills. This dissociation between learning systems confirms that the ability to learn motor skills is retained even in the presence of profound declarative memory loss. Clinical strategies that can be effective when working on motor skill acquisition with individuals who have profound short term declarative memory loss include task-specific training that focuses on the direct acquisition of skills, adaptation of daily routines or the environment such that cues for functional skills can be provided that do not require declarative recall (e.g., memory boards, prearranged functional setups, pictures), and monitoring responsiveness to therapeutic interventions by more sensitive measures of motor performance such as measurement of the time to complete tasks (25).

Motor skill acquisition occurs as a result of practice. The process of motor learning occurs in stages. Fitts and Posner (26) described three stages of motor skill acquisition. The *cognitive* phase is the initial phase of learning where the learner develops the execution requirements of the skill to be learned. During the *cognitive* phase, the learner has frequent errors and variable performance as he/she develops an understanding of what to do. The learner is dependent on visual and verbal environmental cues to organize the movement. As errors decrease, other forms of feedback such as kinesthetic information will be used for error detection and correction. In this early stage of learning, therapists serve as important sources of augmented verbal, visual or tactile feedback. Feedback that provides information of movement outcome is knowledge of results (KR) and information of movement errors is knowledge of performance (KP) (27). When a therapist reports the time it took to complete a 10-meter walk they are providing KR; a description of the gait deficits during that walk is an example of KP. Due to the high cognitive and attentional demands during this initial phase of skill acquisition, practice in an environment with few distractions is recommended. This is particularly relevant when working with individuals with brain damage who have impairments such as slowed information processing, attention deficits, and high distractibility.

With additional practice, the learner shifts to the *associative* phase of learning. In this phase, the learner shifts from what to do to how to best complete the action. The learner begins to rely less on visual and verbal cues and attends to kinesthetic cues in order to develop an internal reference of correctness. As kinesthetic awareness develops, the learner has a greater ability to detect movement errors and their consequences. After extended practice, the learner shifts to the *autonomous* phase in which motor tasks are performed more automatically and with less error. During this phase, cognitive effort is less and attentional demands directed to the task are reduced. Patients with brain injury can be introduced to more environmental complexity and distraction as they advance to these later phases of skill acquisition.

In summary, motor skill learning is a purposeful, problem-solving thought process in which the learner develops the coordination of perception and action in order to perform motor skills efficiently and effectively (28). Physical practice of a motor skill is the most important requirement in order to promote skill acquisition and motor learning. Therapists are instrumental in setting up the therapeutic learning environment in such a way as to promote the process of skill acquisition. Understanding that motor learning occurs in stages that have varying cognitive demands is especially important when planning a therapeutic session for someone with brain injury. In addition, it is important to be aware that the level of performance proficiency (i.e., cognitive, associative,

autonomous) will vary with the task and environmental demands (29). In other words, a functional task such as a wheelchair transfer may be performed at an autonomous level in the structured and quiet atmosphere of an individual treatment room. However, on the nursing unit where environmental demands are high or during a car transfer where task demands are more difficult performance proficiency may regress to a lower level until sufficient practice with these additional challenges has occurred.

### Principles of Motor Learning

Motor learning is a process associated with practice or experience that leads to a relatively permanent change in the ability to produce skilled movements (27). However, in the clinic, learning processes are not directly observed since learning is a reflection of internal neural processes such as enhanced synaptic efficacy within motor-related neural networks. Motor performance is the level of skill execution or how a person completes a movement or functional task. Motor performance is the directly observable action. Motor learning is inferred when an individual reliably and accurately performs a motor skill in various settings and across various points of time. We can infer that an individual has truly learned a motor skill when motor performance can be retained or transferred to a novel situation. The motor performance versus motor learning distinction is very important since conditions of practice and feedback, which can positively impact motor performance, can interfere with the cognitive processes that are required to promote motor learning.

Practice and feedback are two of the most important training variables that can affect motor performance and learning. Motor learning research of both healthy controls and individuals with brain damage demonstrates that practice and feedback can be manipulated in such a way that performance gains during training can be very high; yet, measures of learning such as performance during a retention or transfer test can be detrimentally affected. Clinically, we observe motor performance as a patient practices a task during a therapy session. How would a therapist determine if the patient learned the motor task? In the clinical setting, a retention test would be the observed performance on the following therapy session with no feedback or cueing provided. Performance at this moment would reveal the task-related learning that occurred from the previous therapy session. In contrast, a transfer test reveals the generalizability of what was learned in one condition to another similar but different condition. For example, it has been demonstrated in individuals with stroke that practice in a static balance activity did not transfer to the balance requirements needed during walking (30). In contrast, practice of treadmill walking at speeds closer to normal walking speeds

results in very good transfer in that walking speed increases are observed overground (31).

Practice conditions can be manipulated to vary the presentation of tasks (i.e., practice schedule) across a training session or the presentation of feedback within a training session of a particular task. Conditions of practice or feedback that invoke greater cognitive effort appear to be more effective for motor learning. Cognitive effort involves the perceptual and motor as well as decision-making processes that occur during skill acquisition (32). When cognitive effort is high during task practice, performance may be degraded; however, retention performance is better compared to task practice with less cognitive effort. Cognitive effort as a construct that underlies motor learning processes has profound implications for the generalizability of motor learning principles derived from young, healthy adults to motor skill learning in individuals with impaired cognitive processing. What is the interaction between practice or feedback conditions that require greater cognitive effort in individuals who have impaired cognitive ability? It is not yet clear what the impact of cognitive processing deficits post-brain injury will have on mental processes associated with motor learning. The following section will review the limited literature that investigates the manipulation of practice and feedback on motor learning in individuals with brain damage.

*Effects of Practice Conditions* Structuring the practice session includes the determination of the tasks to be practiced and the order of this task practice during the therapy session (33). Part-task vs. whole-task practice is one example of a practice schedule where either a task is practiced in its separate components or is practiced in its entirety. Consistently, it has been demonstrated in young, able-bodied individuals that the effectiveness of whole-vs. part-practice relies upon the nature of the task being learned (34). If a task is serial in nature, a part-task practice schedule can be effective. A serial task is a task that can be broken into discrete tasks that when ordered appropriately result in a meaningful functional outcome. For example, a patient learning to brush his teeth in the morning must learn to unscrew the toothpaste and apply it to the brush, move the brush to clean his teeth, and reach for a glass in order to rinse his mouth. Each discrete component of this functional task sequence can be practiced individually then practiced as a whole. In contrast, continuous tasks such as walking, pushing a wheelchair, or steering a car cannot be parsed into discrete components since successful task performance requires interaction and responsiveness to environmental conditions.

Variable and random-order practice are two practice conditions that have been demonstrated to be more effective for motor learning in young, able-bodied populations. Variable practice reflects the variety of conditions

in which a task is practiced such as walking on a treadmill at different speeds or practicing a transfer to different surfaces. This is in contrast to constant practice where the same task and conditions are repeatedly practiced. Theoretically, variable practice is a more effective method of invoking the cognitive processes to establish a motor program and the flexibility of processing needed to parameterize this program to meet environmental goals (35). Unfortunately, there are very few motor learning studies in populations with brain-damage that have tested these hypotheses. In fact, there is some evidence that variable practice effects in healthy, able-bodied populations may not be as applicable to individuals with profound declarative memory impairments (18) or motor deficits (31).

Random order practice is a practice schedule in which the order of, for example, 3 different tasks are scheduled throughout a therapy session. This is in contrast to a blocked schedule where the 3 tasks would be ordered and practiced in a block such that practice of task 1, is followed by task 2 and so forth. The effectiveness of random-order practice in comparison to blocked practice has been attributed to the *contextual interference effect* (36, 37). Contextual interference is the cognitive interference introduced when several tasks are practiced together. Random practice induces a form of forgetting that requires the learner to reconstruct the motor memory from a previous, but not immediately preceded, practice trial. The evidence for random-order practice in individuals with brain injury is limited and not consistent. Random practice has been demonstrated to be effective in individuals with stroke learning a series of functional grasps (38) but has not been investigated in individuals with more profound declarative memory and cognitive processing deficits. It is not clear how brain injury that affects various higher-level cognitive processes such as memory and attention may influence practice condition effectiveness. Further work is needed to determine if practice conditions that promote deeper levels of information processing will be as effective in individuals with brain injury that have information processing deficits.

**Effects of Feedback** Feedback has a powerful influence on motor performance. A patient learning a motor skill receives intrinsic feedback from visual, auditory, and proprioceptive systems that may or may not be impaired due to brain injury. In addition, a patient receives augmented feedback from the therapist in the form of KR or KP as the therapist provides verbal, visual, or tactile information during a therapeutic procedure or functional training session. Augmented feedback can interfere with the more permanent learning effect that one hopes to achieve with practice. If given too frequently or continuously, feedback can interfere with the problem solving thought process that should occur during practice and instead “guide” the patient to the optimal response (39). Studies

that have examined the effects of feedback in healthy subjects (40), older individuals (41, 42), individuals with stroke (43), and TBI (44) demonstrate that post-response feedback (feedback provided after the skill is performed) given with less frequency can result in motor performance during a retention or transfer test that is more accurate or consistent than feedback provided more frequently or concurrently. In these types of studies, feedback is provided after every trial (100%), with reduced relative feedback (i.e., 50% of trials), or concurrently in which feedback is provided at the same time as the task is performed.

Concurrent feedback consistently degrades learning compared to post-response feedback with less frequency (45). Yet, therapeutic interventions that use biofeedback, computer-generated feedback, or continuous physical guidance by a therapist are examples of concurrent feedback that is typically observed in the clinical environment. One method that appears to be particularly effective in clinical settings to promote motor learning is the use of a faded feedback schedule in which the relative frequency of feedback is decreased within or between practice sessions. With a faded feedback schedule, feedback presentation is high during early learning and then decreased in frequency in the later phases. In this way, feedback is provided in the early stages when the learner needs much information to learn what to do and how to perform the task but feedback is faded as the learner is encouraged to develop the problem solving and self-discovery needed to actually learn a motor skill.

**Summary** The importance of practice, the effective scheduling of practice and the frequency of feedback are important principles of motor learning that can be applied to the treatment of individuals with brain injury. However, evidence guiding clinical application is limited and at times inconsistent. In particular, there is a need for motor learning studies that examine the interaction between the cognitive processes invoked during the motor learning process with the cognitive impairments that result from brain injury. Sherwood and Lee (32) propose that the depth of cognitive processing and the degree of cognitive effort have a profound effect on motor learning processes. This has implications for the application of motor learning principles in the rehabilitation of individuals with brain damage. Individuals with profound cognitive impairments in attention and memory may respond differently to conditions of practice or feedback frequency that require greater depths of information processing or cognitive effort. Further work is needed to understand these relationships; however, therapist can take concepts presented here and apply it to the clinical setting. Blocked practice and frequent feedback, which have lower information processing demands, may be more appropriate for individuals with severe cognitive processing deficits. However, over the course of recovery,

conditions of practice and feedback that require greater cognitive effort would be appropriate.

### Principles of Exercise

Therapeutic exercise is the method most commonly used to address mobility problems after brain injury. Therapeutic exercise incorporates exercise principles into the design of therapeutic interventions in which the goal is to increase functional performance and decrease specific movement-related dysfunction. Traditionally, therapeutic exercise programs have been designed to remediate impairment specific mobility problems. For example, if range of motion is limited due to muscle shortening, exercise techniques can be used that will effectively lengthen the shortened muscle. While impairment-focused interventions may be effective in the rehabilitation of specific impairments (evidence for impairment-focused interventions will be discussed later in the chapter), there is building evidence from meta-analysis that impairment-focused interventions have no effect on functional performance (46).

A recent trend in therapeutic exercise is to incorporate sport physiologic training principles in the design of exercise programs that increase aerobic capacity and strength in individuals with brain damage (47, 48). This is an important consideration since the dosing of exercise can influence treatment outcome. Task-specificity (what is the nature of the task or skill to be learned?) and training intensity (what is the frequency, duration, time, and demand of the activity?) appear to be 2 important factors that affect therapeutic exercise effectiveness after brain injury.

*Task-Specific Training* Since the writings of Bernstein in the early 1900's (49), the importance of movement and task-specific learning has been well recognized in the psychological sciences. It has only been in the past 10–15 years that the emphasis on task-specific training has been incorporated into the rehabilitation setting.<sup>1</sup> The effectiveness of task-specific training derives from the specificity of learning hypothesis proposed by Henry in the 1950's who suggested that the most effective conditions for motor learning occur when performance during practice is well-matched to the performance requirements needed during retention or transfer conditions (50). Motor learning reflects a neural specificity of practice since motor skill acquisition involves the integration of

the sensory and motor information that occurs during practice, and ultimately, leads to the sensorimotor solution that results in accurate, consistent, and skillful movements (27).

The importance of repetitive, task-oriented practice in the recovery of upper limb function (51–53) and walking (31, 54–57) has been consistently demonstrated in clinical trials of stroke-related brain damage and is beginning to emerge in TBI populations as well (58–61). In these studies, interventions are designed that involve specific task practice that incorporates the upper limb in various functional activities or in repetitive activity such as walking on a treadmill.

A recent and comprehensive systematic review compiled by Van Peppen et al. (46) of physical therapy interventions post-stroke demonstrated strong evidence for greater patient benefit due to functional task practice than impairment-focused interventions. Functional improvement was associated with interventions such as aerobic training, constraint-induced movement therapy, transfer training, and treadmill training with or without body weight support. In contrast, exercise programs that focused on muscle strengthening, muscular re-education with biofeedback or neuromuscular stimulation showed improved impairment level outcomes such as strength and range of motion but failed to result in significant functional outcomes. In addition, Van Peppen et al. (46) demonstrated no evidence for improved functional outcomes to support the use of neurophysiologic treatment approaches such as neurodevelopmental treatment (NDT), proprioceptive neuromuscular facilitation (PNF) or Brunnstrom (62–64).

Our understanding of the mechanisms that subserve functional recovery and responsiveness to task-specific training is elucidated by eloquent animal work that demonstrate that repetitive task practice that involves the acquisition of a motor skill results in neuroplasticity in both synaptic and neuronal morphology and in cortical reorganization (6, 65, 66) These findings of experience-dependent neuroplasticity are corroborated in humans with brain damage through recent neuroimaging studies that use transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI) to demonstrate the potential for cortical reorganization as a result of task-specific therapeutic interventions for both upper limb and lower limb recovery (67–70).

*Training Intensity* Time spent in exercise training and increasing the difficulty or physiologic demands of the exercise session are examples of methods to increase training intensity. Exercise dosing can have differential effects that vary as a function of the time in the activity (min/day), frequency of sessions (times/wk) and the duration of training (weeks of training). Kwakkel et al. (71) demonstrated that specific skills training post-stroke for

<sup>1</sup>Note that task-specific training is distinguished from ADL training. Task-specific training implies that the training event is designed to improve motor skill acquisition in a specific task. ADL training implies that the training event is designed to decrease the level of physical assistance to complete a functional task; therefore, ADL training may allow the use of compensatory strategies or assistive devices in order to enhance task completion.



30 min/day, 5 days/wk for 20 wks in addition to a standard rehabilitation program was most effective if the specialized training was specifically focused on active arm or leg focused training. Winstein et al. (53) have also demonstrated the preferential effect of additional therapy time in functional task training. The added significance of this study is that functional training in the early rehabilitation period post-stroke resulted in significant differences in both strength and function at 9 months post-injury compared to strength training or usual care groups. This study illustrates the impact that early functional training in the period immediately post-injury may have on future limb use and function later in the recovery process.

A recent systematic review specifically investigated the effects of exercise intensity as measured by time in therapy on ADL, walking, and dexterity in patients with stroke (72). The results of this meta-analysis suggests that more intensive therapy that includes approximately 16 hrs of additional task-specific training in the first 6 months post-brain injury particularly dedicated to lower limb and ADL activities is more effective than standard therapy programs. Limitations of this meta-analysis include the inability to determine the precise treatment contrast that separates the longer time in therapy from the control comparison. At this time there is insufficient literature in TBI populations to conduct a meta-analysis; however, there is some evidence that the findings from stroke may be somewhat generalizable to individuals with TBI. Eng et al. (73) in a prospective study in the inpatient rehabilitation setting compared mobility outcomes between patients with stroke and TBI. Overall, patients with TBI had higher mobility status at admission and discharge; however, the improvement in mobility status per day was not different between the diagnostic groups. Cifu et al. (74) specifically examined the effect of therapy intensity (time in therapy/ length of stay) and found that therapy intensity predicted the amount of motor function improvement a discharge. While the level of evidence may not be as high as the evidence from stroke, there is clearly a trend that shows similar responsiveness in patients with TBI. Collectively, this literature reflects the need for studies that investigate the optimal dosing of exercise programs designed to improve mobility especially in populations with brain beyond stroke.

Incremental increases in task difficulty and increasing the physiologic demand of the exercise are additional methods to manipulate training intensity. Adaptive task practice is a method whereby the therapist adjusts the difficulty of the task as they observe performance and provide feedback during practice. Task difficulty is adjusted such that the patient experiences progressive challenge across training. Adaptive task practice is one of the practice strategies used in CI therapy as the optimal movements develop or a “shaped” during therapy. Strong evidence exists for CI therapy as a treatment to increase dexterity

of the hemiparetic arm and appears to be related to the high intensity dosing of task-specific upper limb training (46). Case study series in individuals with TBI using a modified CI therapy approach are beginning to demonstrate a similar responsiveness to this type of training (60).

Increasing physiologic demand is another effective strategy to increase training intensity. In studies of treadmill training with and without body weight support, it has been demonstrated that treadmill training at higher speeds is more effective than training at constant or variable speeds that are within the range of the patient’s typical overground walking speed (75, 76). In addition, fast walking results in improvements in body and limb kinematics and muscle activation patterns in individuals that have impaired walking due to hemiparesis (77). Training within a task at maximum capability is one of the tenets of training specificity and appears to be applicable to individuals with brain injury relearning a functional task. The equivocal evidence found in the recent Cochrane review of treadmill training with or without body weight support may be due to the high degree of variability between studies in the frequency, duration, and timing of the intervention as well as the level of physiologic intensity used across studies (78).

*Summary* Task-specificity and intensity are important principles of exercise that can be applied to the treatment of individuals with brain injury. There is strong evidence that intensive, functional task training is effective in individuals with stroke-related brain damage; however, there is limited (yet developing) evidence in populations with TBI. Most likely, principles of exercise incorporated into therapeutic interventions will extend to other populations with brain damage such as those with TBI. It is unknown if cognitive and behavioral problems, common post-TBI, will interfere with the compliance needed to achieve the desired training effect.

## THE LINK BETWEEN ACQUISITION OF SKILLS AND AVAILABLE RESOURCES

At this point, we return to the rehabilitation model proposed by Quinn and Gordon (79) (Figure 50-1). This chapter has focused on the acquisition of skill including the evidence that neuroplasticity and neurorecovery are promoted through the skill acquisition process, conditions of practice and feedback frequency affect the retention and generalizability of motor skill learning, and training intensity and specificity appear to be important parameters that drive functional training effectiveness. Skills are required in order for our patients with brain damage to participate in desired roles related to self-care, social and recreational pursuits, and occupation. However, post-TBI there is a myriad of physical, behavioral, and cognitive

limitations that contribute to the functional deficits. Typically, rehabilitation specialists classify these limitations as impairments that have to be remediated. The perspective developed by Quinn and Gordon suggests that the goal of therapy is to determine what resources the patient needs to successfully accomplish the functional task. In essence, the diagnostic challenge for the therapist is to identify the impairments that prevent functional task performance and develop an intervention program that develops the necessary resources to successfully complete the task. This section of the chapter will address the therapeutic interventions and strategies used to develop patient resources and address impairment level problems.

**Behavioral Treatment Strategies**

In the days, weeks, and months after TBI, patients present with a variety of potential behavioral disorders that may impact their ability to participate in therapy. This can be compounded by organic deficits in cognition (e.g., confusion and disorientation, decreased short term memory, decreased problem-solving and reasoning ability, delayed processing, motor and verbal disinhibition, lack of initiation and concrete reasoning), perception (e.g., visual, auditory or tactile hyper- or hypo-sensitivity, neglect, visual-field deficits, right-left discrimination problems), and communication (e.g., expressive or comprehension aphasia, decreased understanding, delayed responsiveness) as well

as their personal reactions to injury and disability such as loss of control, frustration and anger, lack of insight, and depression. The challenge for the therapist working on mobility issues is to adjust performance expectations and to adapt the therapeutic learning environment. The Table 50-1 summarizes common therapeutic strategies that can be applied as the patient progresses through the various behavioral and cognitive phases associated with TBI recovery.

The overall therapeutic goal is to progress the patient through the various stages of cognitive function recovery through systematic and graded stimulation and activity (29). The following descriptions provide an overall behavioral strategy that would be appropriate as specific mobility training or preventive maintenance of musculoskeletal deformity is being applied. It is important to note that the stages of motor learning discussed earlier have applicability within each of these stages particularly at the mid- and high-level management phases. Motor performance proficiency increases as the learner moves from the cognitive, associative, and autonomous phases of skill acquisition. Similar strategies such as monitoring environmental distraction and task complexity apply as well when an individual with brain injury is progressing through the levels of cognitive function (80, 81).

It is important to note the level of evidence for most recommendations on cognitive management used for physical rehabilitation are primarily at the level of clinical expertise. A recent Cochrane review of sensory stimulation for individuals with TBI in a coma or vegetative state revealed that most of the literature in this particular area of cognitive-physical rehabilitation is primarily at the level of case study or case series (82). Three studies met inclusion criteria for an RCT; however, there were serious methodological limitations that led the authors to conclude that there was no reliable evidence to rule in or out the use of sensory stimulation in patients in coma. Given the need for additional RCT's that address the issue of cognitive and physical management post-TBI, the following summarize what is regarded as best available practice in this area using the Rancho Los Amigos Levels of Cognitive Function (LOCF) Scale to delineate low-, mid-, and high-level cognitive groups (80).

*Low-Level Cognitive Management* Patients who are considered within the LOCF levels of I, II, and III have low-levels of responsiveness that range from unresponsive to any stimulation (LOCF I), generalized response that is limited and non-purposeful (LOCF II), to localized responsiveness in which the patient may follow simple commands (LOCF III). This decrease level of responsiveness is often accompanied by severe postural tone and paralysis that can lead to secondary musculoskeletal impairments. Specific strategies to address these secondary impairments will be discussed later. In addition, to preventing complications due to immobility and impaired

**TABLE 50-1**  
*Behavioral Treatment Strategies*

LOCF	RECOVERY PHASE	APPROACH
I, II, III	Minimal response	Sensory stimulation Preventative maintenance Monitoring response to early mobilization
IV	Confused, agitated	Structured environment Directed activity Monitor response to stimulation Brief, frequent activity changes
V, VI	Confused	Structured environment Directed activity Consistent approach Complexity to tasks varied gradually Environmental distractions varied gradually
VII, VIII	Automatic	Reduce structure Greater self-monitoring Progressively challenging tasks

LOCF – Levels of Cognitive Function from Rancho Los Amigos Rehabilitation Hospital (Hagen, 1079).

motor control therapists, in collaboration with other team members, usually begin some form of sensory stimulation program to encourage arousal and responsiveness. Once the patient is medically stable, upright mobility activities are initiated progressing from bed mobility to upright postures in a wheelchair or tilt table. Observationally, changes in posture and upright positions appear to be effective in evoking increased levels of responsiveness in patients in these lower levels.

**Mid-Level Cognitive Management** The transition from unresponsiveness to LOCF IV is often accompanied by confusion and agitation. A patient at this level is easily confused and disoriented and may present with aggressive and inappropriate behavior. His responses during this phase appear to be due to internal confusion. During this phase, the patient cannot readily engage in self-care activity and episodes of incontinence are frequent due to lack of internal and external awareness. The therapeutic strategy at this phase is to provide a structured and safe environment with minimal distraction that can allow the patient to move about. Within this structured environment, brief, directed activity can be introduced. Frequent, short treatments that are interspersed across the day would be the ideal therapy schedule for a patient in this phase.

Patients' post-TBI at LOCF V and VI are non-agitated but continue to present with confusion and profound declarative memory deficits. At LOCF V, the patient responds to commands and is more alert but is easily distractible with difficulty concentrating on tasks. Agitated outbursts and inappropriate verbal responses still occur when the patient is frustrated. At LOCF VI, that patient has more consistent goal-directed behavior but needs cuing. Greater participation in ADLs is evident as the individual is developing greater awareness of self and others. This level is associated with the period of post-traumatic amnesia in which the ability to develop new declarative memories is seriously impaired. The Rancho Cognitive levels state that during these phases individuals cannot learn new information. However, the distinction between the explicit (declarative) and implicit (non-declarative) memory systems would suggest that patients during post-traumatic amnesia do have the capability to learn new motor skills, and in fact, has been demonstrated in individuals' post-TBI during post-traumatic amnesia (23, 24).

The most effective therapeutic strategies during this phase would include task-specific training in structured environments. Treatment approach at this level would encourage successful performance through adaptive task practice in which task practice is challenging, yet, successful. The expectation is that repetitive task practice during this phase of recovery would lead to a gradual improvement in motor performance as the patient acquires motor skills that may be independent of any

verbal recollection of the task training. For patients with confusion, a consistent approach to the daily schedule, treatment setting, activities, instruction, and team members is most effective. Task complexity and changes in the structure of practice (i.e., increased variability) and feedback (i.e., decreased frequency) can be progressed as the patient's cognitive status improves.

**High-Level Cognitive Management** The progression from the previous levels to LOCF VII and VIII is marked by improvements in short term memory with more appropriate and purposeful behavior. During this phase, there is less confusion, better recall, and increased self-awareness and interaction with others and the environment. However, limitation in insight, abstract reasoning and problem solving can still exist, particularly for those in LOCF VII. At this level, it is realistic to expect completion of ADLs with relative independence. Therapy focuses on the tasks and skills needed to facilitate community integration. This phase is primarily focused on skill acquisition in the tasks that will assist the individual to participate in their desired self-care, social, occupational, and recreational goals.

### **Physical Impairment-Focused Interventions**

Mobility impairments after brain injury are either directly related to the damage of neural structures such as impairments in voluntary movement, abnormal tone, and balance or are secondary impairments that result from these neural system impairments. Secondary mobility impairments result in limitation of the musculoskeletal system such as muscle contractures, joint mobility restrictions, and disuse weakness. Both neural and musculoskeletal impairments can be major contributors to functional deficits after brain injury. The following section provides a brief overview of current therapeutic strategies to address these problems.

### **Neural System Impairments**

**Voluntary and Purposeful Movement** Impairments in voluntary movement associated with TBI can be due to an upper motor neuron weakness syndrome that includes inability to do selective joint movements out of synergy, decreased force production, and impaired initiation of purposeful voluntary movement. The primary mechanisms for these movement deficits post-TBI can be attributed to diffuse axonal injury due to scattered white matter infarctions in the descending motor pathways, focal cortical contusions or deep cerebral hemorrhage that results in direct damage to the corticospinal tract as it passes through the striatocapsular region, and transtentorial herniation where compression of motor pathways in the upper brain stem can occur (83). Diffuse axonal injury

and/or major brainstem contusion can result in low levels of consciousness in which reflexive movement patterns within decorticate and decerebrate postures can result from motor output of subcortical motor brainstem systems that include the rubrospinal, reticulospinal, and vestibulospinal systems (84).

In contrast to stroke where 70% of all stroke survivors will present with a motor hemiparesis (85), only 17% of patients post-TBI will have arm/hand paresis with synergistic movement and of these individuals motor recovery is good such that only 3% will have synergistic hemiparesis at 4 months post-injury (83). The predominant motor deficit in patients post-TBI is impaired force production leading to decreased power generation and strength and impaired integration of voluntary movement with the other cortical, subcortical, and cerebellar motor systems involved in the planning, initiation, completion and retention of accurate and consistent goal-directed movement. Weakness and impaired power generation can be a major factor along with sensory integration and cognitive deficits that interfere with performance of mobility tasks. The differential diagnosis and treatment of movement dysfunction after brain injury requires the therapist to determine what are primary contributors to impaired task completion (i.e., force generation, synergistic movement), how can these primary contributors be addressed (i.e., strength training, muscle re-education), and how can the learning environment be structured to result in the acquisition of skill when considering both the cognitive and motor deficits of the patient (i.e., task-specific training).

There are numerous therapeutic strategies employed by therapist to address issues of neural motor control that can vary in emphasis across the recovery continuum from the acute care phase (86) where lower level management strategies are needed to later in the recovery process where the focus is to incorporate motor control strategies with task training (81, 87–89). Current approaches to muscle re-education and therapeutic exercise use an interactive systems model that emphasizes that task accomplishment emerges from a complex interaction of biomechanical, motor, and sensory effects that are modified by environmental constraints (90). Typically, therapists interact with the patient as they manipulate the mechanical demand of the task within the sensorimotor conditions that optimize task performance.

Traditionally, neurophysiologic therapeutic approaches such as neurodevelopmental treatment (NDT) (91), proprioceptive neuromuscular stimulation (PNF) (92), and the Brunnstrom approach (93) were commonly used to facilitate motor and postural control. These approaches were derived from the neurophysiologic understanding of the time such as the hierarchical organization of the nervous system, that proprioceptive afferent sensory stimulation can be used to modify abnormal tone and

facilitate a patient's movement pattern, and that recovery from brain damage occurs in a predictable sequence that corresponds to development (94). With current advances in neuroscience (5) and greater understanding of motor control (95) as well as the trend for evidence-based practice, there is building consensus that the traditional neurophysiologic treatment approaches are not effective compared with usual care that emphasizes functional training (46). It would be remiss to treat patients with a traditional neurophysiologic treatment approach alone since it appears that these approaches emphasize impairment-focused intervention and have not been shown to be effective in improving functional gains. However, important therapeutic principles have emerged from these traditional neurophysiologic approaches that continue to influence practice today. The importance of proximal control and midline alignment, the use of resistance and developmental postures as ways to increase demand needed for functional tasks, and the quantification of recovery as patients develop more isolated joint movement and control all derive from these approaches. Current best practice would incorporate these important therapeutic principles with our understanding of motor learning and exercise physiology to promote skill acquisition in our patients with brain injury.

*Abnormal Muscle Tone* Clinically, therapists are confronted with two major problems related to the impaired regulation of muscle tone. Abnormal muscle tone includes problems with velocity-dependent increases in phasic stretch reflexes associated with the upper motor neuron syndrome (i.e. spasticity) (96) and abnormal postural control interfering with the ability to maintain upright head, neck, and trunk postures against gravity (86). Pierson (97) describes a wide range of clinical assessment tools that can be used to assess treatment effectiveness and functional outcomes as it relates to abnormal tone particularly spasticity. These tools include goniometry to assess range of motion limitations that can result from muscle imbalance, the modified Ashworth Scale that is an ordinal scale to quantify tone intensity, and functional tests such as the Jebsen Taylor Hand Function test, gait speed, and the Berg Balance scale to determine the effects of abnormal tone on function. These outcome measures are commonly used; however, a recent review of the reliability and validity of spasticity assessments suggest that further work is needed to develop more objective measures as well as measures that capture the real-world impact of spasticity on function (98).

The approach to abnormal tone management is twofold. One is to address the primary issues related to spasticity and postural control by providing therapeutic interventions that attempt to decrease tone or increase upright control in functional postures such as sitting and standing. The second approach is to address the secondary

musculoskeletal impairments that can occur when severe and unrelenting increases in abnormal muscle tone result in muscle contracture and joint deformity. Specific approaches to address these secondary tone-related impairments will be discussed in the next section.

Therapeutic interventions that use weight bearing through the extremities and trunk are often used in various functional positions to decrease tone as the patient develops appropriate motor control to maintain upright postures and to complete functional tasks (86, 88). The goal of the therapy is to facilitate more effective motor unit recruitment, and due to the task-oriented nature of the training, appears to be more effective than interventions that focus on the reduction of spasticity alone. For example, in a recent double-blind, placebo-controlled multi-site RCT, botulinum toxin intramuscular injections reduced muscle tone in patients with upper limb spasticity after stroke but there was no change in disability or quality of life (99). In a similarly controlled RCT, botulinum toxin injections to the gastrocs were effective at reducing muscle tone and limb pain but were no more effective than placebo in improving gait function (100). In both studies, no specific splinting or physical therapies were incorporated into the treatment. One explanation for the lack of functional improvement is that treatment only focused at the impairment level (i.e., the reduction of muscle tone) and did not potentiate the benefit of tone reduction with the process of skill acquisition. More effective approaches to tone management may include the integration of pharmacologic interventions with the task-specific training required to make significant functional improvements.

*Balance and Vestibular Disorders* Balance and vestibular disorders after TBI can be due to damage of the peripheral vestibular sensory apparatus or central structures that respond to the vestibular sensory inputs such as the vestibular nuclear complex, central pathways of the vestibulo-ocular and vestibulospinal reflexes, the brainstem, and cerebellum (101). Peripheral vestibular dysfunction after TBI can be reduced (hypofunction) which results in vertigo, dysequilibrium, and impaired gaze stability if the damage is unilateral. If bilateral, patients may have less severe complaints of vertigo but present with severe dysequilibrium and gait ataxia. Trauma to the head can also result in benign paroxysmal positional vertigo (BPPV) caused when otoconia either are displaced into the semicircular canals or is floating in the endolymph. BPPV results in distorted vestibular function that is gravity-sensitive; therefore, episodes of severe vertigo and positional nystagmus occur with head position changes. Central vestibular disorders can commonly occur as a result of diffuse damage to white matter tracts that interact with vestibular areas of the brainstem and the cerebellum. Severe episodes of vertigo and dizziness are not

as common with central vestibular disorders. Patients will usually have a wide range of symptoms, which include constant feelings of vertigo that are also accompanied by nausea, nystagmus, ataxia, or dysequilibrium. Whether from central or peripheral causes, balance deficits and dizziness have been identified as major factors affecting functional prognosis and return to work after TBI (102, 103).

Patients post-TBI commonly present with gait instability and are at high risk for falls. Balance deficits can be a result of the combined effects of visual, somatosensory, and vestibular impairments as well as motor control deficits that result in weakness and incoordination. The Dynamic Gait Index (DGI) is a clinical tool that can be used to assess fall risk in individuals with balance disorders (90). Whitney et al. (104) demonstrated that gait instability as measured by the DGI was related to falls history. Individuals with vestibular disorders that were either from peripheral (e.g., BPPV, labyrinthine concussion, labyrinthitis), central (e.g., stroke, head trauma, cerebellar dysfunction) or combined peripheral and central vestibular dysfunction were 2.58 times more likely to fall if they scored  $\leq 19/24$  on the DGI.

Vestibular rehabilitation post-TBI can include vestibular adaptation exercises such as gaze stabilization exercises, balance retraining, sensory organization exercises with progressively more difficult static and dynamic activity, and canalith repositioning maneuvers (101). There is good evidence that vestibular rehabilitation that incorporates various balance retraining strategies that are designed to address specific patient problems can be effective (105, 106). The two exercise approaches used for the treatment of vestibular hypofunction include vestibular adaptation exercises to improve gaze stability and balance exercises that foster the use of visual and somatosensory information to improve postural stability (see Herdman (105) for detailed description of vestibular, balance, and gait exercises used for balance rehabilitation). Canalith repositioning maneuvers are specific techniques used to treat patients with BPPV (107). It is beyond the scope of this chapter to discuss the appropriate application of all these various balance interventions since they are designed to address specific vestibular deficits based upon the patient's history, age, and diagnosis. Excellent sources are available to provide greater background in this rehabilitation specialty area (105, 108).

### **Musculoskeletal Impairments**

*Muscle Contracture and Joint Mobility* Impaired voluntary motor control and spasticity are the primary cause of muscle contracture and joint deformity after TBI. Hypertonia in combination with immobility due to paralysis and altered mechanical properties of muscle and connective tissues due to disuse can result in severe deformity of the upper and lower extremities. In addition, heterotopic

ossification can further complicate joint mobility management. Common patterns of deformity that result from spastic motor patterns includes shoulder adductor/ internal rotation, elbow flexion, forearm pronation, wrist and finger flexion contractures of the upper limb and equinovarus foot with clawed toes, valgus foot, stiff or flexed knee, and hip adductor and flexor contractures of the lower limb (109). Spastic deformities interfere with bed positioning, sitting and standing, transfers and walking as well as self-care activities such as hygiene and dressing. In addition to interfering with function, spastic deformities can be a major source of pain (97). The cumulative effect of these secondary musculoskeletal impairments can seriously impact quality of life or the potential for recovery especially for individuals who have been in coma for extended periods of time.

The primary therapeutic goal is to prevent or correct muscle contractures. Various preventative methods are employed in the acute care setting immediately post-injury such as performing passive range of motion and stretching or using preventive bed position including the use of wedges, splints, and pillows to improve limb alignment (86, 110). Various therapeutic interventions are effective to increase passive range of motion or to prevent its loss and include stretching (111, 112), serial casting (113, 114), dynamic splinting (110, 115), orthotic management (116), and, in combination with these types of physical approaches, pharmacologic management such as motor point blocks (116), and intrathecal baclofen (117). In severe cases, when more conservative management has not been effective, surgical management for tendon lengthening or releases may be indicated (110).

*Weakness and Deconditioning* One area that is beginning to receive more study is the effect of immobility on work capacity in individuals with brain injury. Peak exercise capacity and cardiorespiratory fitness of individuals with moderate to severe brain injury is reported to be 60–70% of the capacity of normal healthy adults of similar age (118). It is common in the acute phase that patients with TBI are confined to bedrest for days, weeks, or months depending upon the initial brain injury severity. The adverse effects of prolonged bedrest are well documented in humans but little attention has been given to the additive effects of immobility to chronic disease or injury (119). Immobility due to bedrest as well as a reduction in physical activity results in decreased muscular strength and aerobic capacity that leads to reduced work capacity. Additionally, prolonged immobility can result in osteopenia, which can interfere with fracture healing for patients who may also present with multiple fractures in addition to the brain injury (120).

Thirty days of bedrest can result in 18–20% reduction in knee extensor peak torque; however, strength can recover within 92% of pre-bedrest levels within 30 days

after bedrest (120). Findings such as these highlight the importance of active muscle contraction during bedrest and the introduction of early intermittent ambulation and physical activity to attenuate the effects of immobility in patients with TBI. Responsiveness and tolerance of individuals with moderate to severe TBI to aerobic or circuit training has been demonstrated in both the acute and sub-acute phases post-TBI (47, 48). Peak work rate improved in patients with TBI recruited within  $24 \pm 14$  wks of injury that completed resisted cycling for a goal of 30 min (actual cycling time achieved  $23 \pm 5$  min) at 60–80% age-predicted maximum heart rate for 24 sessions over 8 wks (47). Forty-five minutes of circuit training (combination of aerobic exercise, muscular strength, and endurance training) at 60% age-predicted maximum heart rate for 3 sessions per week for 12 wks increased peak power output and  $\text{VO}_2$  peak in 14 individuals approximately 17 wks post-injury (48). Clearly, exercise and early mobility training are indicated to lessen the impact of secondary causes of weakness and decreased endurance. With proper supervision and monitoring of cardiovascular responses to exercise, individuals with TBI can engage in intensive strength and conditioning training.

## INNOVATIONS IN PHYSICAL REHABILITATION

Constraint induced (CI) movement therapy and the use of treadmill training with body weight support (BWS) are examples of innovations in rehabilitation that are derived from basic science work in neuroplasticity and neurorecovery and incorporate principles of motor learning and exercise into the therapeutic intervention. The therapeutic goal of each of these interventions is to increase skill in functional tasks.

The scientific rationale for CI therapy is derived from studies in non-human primates in which 2 important findings impact the clinical application of this paradigm. First, Taub (121) observed that deafferented monkeys who wore a restraining jacket that constrained the non-affected limb had greater use of the limb than monkeys that were not constrained. However, Nudo (122) demonstrated that greatest amount of motor cortical reorganization and functional recovery occurred in primates who wore the restraining jacket *and* engaged in repetitive skills training. As a result, CI therapy has developed as a therapeutic intervention where use of a constraint device and intensive task practice is used to promote upper limb recovery in individuals who have hemiparesis due to stroke (Fig. 50-3).

The effectiveness of this approach in individuals post-stroke who meet a minimum motor criteria was first described by Wolf (123) and Taub (124) and is currently being investigated in a multi-site, RCT funded by the NIH

(125). The paradigm under investigation includes individuals post-stroke in either the subacute period (4–9 months post-stroke) or chronic period (>1 yr post-stroke) who at a minimum must be able to actively extend the wrist, thumb, and at least 2 other digits 10°. The intervention occurs 5 days/wk for two weeks for 6 hr/day in training with therapist supervision that combines the use of a constraint device (mitt on unaffected hand) with task practice and adapted task practice (shaping). The patient signs a behavioral contract and agrees to wear the mitt 90% of waking hours and to maintain a daily diary of activities. The results of the trial have not been published; however, smaller experimental trials have demonstrated the effectiveness of this intervention and the specific effectiveness of this practice schedule (126–128). Several recent studies have found that a modified CI therapy (Figure 50-3) can be effective after stroke (129, 130) and TBI (60). These researchers found that a modified practice schedule of CI therapy for 3 times/wk for 10 wks for 30 min/day of supervised therapist training in combination with the restraint use 5 dy/wk for 5 hrs/day during patient-identified times



**FIGURE 50-3**

Constraint induced (CI) movement therapy is a therapeutic intervention where use of a constraint device and intensive task practice is used to promote upper limb recovery in individuals with hemiparesis

of high frequency upper limb use results in improved motor function and self-perceived use of the limb. One of the advantages of a modified practice schedule is that it is more compatible with the delivery of services reimbursed for rehabilitation at this time.

Step training on a treadmill with body weight-support (BWS) is a neurotherapeutic intervention used to promote locomotor recovery in individuals with spinal cord or brain injury that is derived from basic science animal research. Adult cats with low thoracic spinal transection recovered the ability to step on a treadmill after training with trunk support and assistance with paw placement (131–133). These findings precipitated a movement in rehabilitation to use body weight support systems in locomotor rehabilitation of humans with spinal cord injury (134–136) and stroke (31, 56) (Figure 50-4). The effectiveness of this type of training is attributed to the intense and



**FIGURE 50-4**

Step training on a treadmill with body weight support is an example of intense, task-specific training that incorporates the repetitive practice of walking

task-specific nature of walking on a treadmill in which the appropriate afferent inputs associated with walking provide the input needed to induce experience-dependent changes in neuroplasticity at spinal and supraspinal levels (137–139).

Despite several investigations of treadmill training with or without BWS in individuals with stroke-related brain injury, a recent Cochrane review found weak evidence supporting the effectiveness of this approach (78). However, what this Cochrane report did reveal is that there is tremendous variability in the time post-injury that the intervention occurred and the frequency, duration, and intensity of the protocols being studied. In fact, subsequent studies that specifically addressed training parameters have demonstrated that training intensity as determined by treadmill speed is an important parameter of training effectiveness (31, 76), yet, none of the studies in the Cochrane review used speeds or other training parameters known to affect exercise effectiveness.

At this time, preliminary work in individuals with stroke-related brain damage does suggest that functional changes in overground walking velocity can occur with a training program that includes a minimum of 12 sessions for at least 3x/wk for 4 wks that results in at least 20 minutes of treadmill walking time at speeds within 1.5 – 2.0 mph (31). Clearly, more systematic work is needed to determine the most effective training parameters for this intervention. There is one study that has demonstrated both the effectiveness and challenge of applying this intervention in individuals with severe brain injury (61). The authors have developed the Missouri Assisted Gait (MAG) Scale to identify the small but significant changes in motor ability during gait recovery of patients with TBI.

What is it about these two rehabilitation innovations that make them distinctly different from usual therapeutic approaches? What is the active ingredient that appears to result in functional changes that appear to be more substantial than in other treatment paradigms? Both interventions incorporate the principles of motor learning and exercise that have been described in this chapter. First, the interventions focus on task practice with appropriate feedback monitored and graded by the therapist. In both CI therapy and treadmill training with BWS, the patient actively engages in task practice for periods of time that are substantially greater than what is typically provided in therapy. Second, the therapies focus on intense, task-specific training. It is more than just the time in task therapy that appears to be effective. The training must be a challenge or engage the patient in higher levels of performance than is normally experienced. Third, task-specificity is incorporated into training protocols that have defined training parameters for frequency, intensity, and duration. In order to achieve a training effect, the patient must engage in enough exercise or task practice,

which is systematically progressed in order to induce a physiologic or neural response. Finally, these interventions address the impairments and deficit in functional skills that are unique to the needs and capabilities of the individual patient.

The Theoretical Model for Neurologic Therapeutic Intervention presented in Figure 50-2 proposes that the theoretical foundation for physical rehabilitation after brain injury is based on the premise that 1) skill acquisition promotes neuroplasticity, 2) motor learning and exercise principles are used to enhance the acquisition and retention of motor skills, 3) skills to be learned are identified through functional task analysis and patient perspective (i.e., the individual's self-perceived goals and expectations), and 4) the differential diagnosis process for therapists involves the identification of the primary and secondary impairments that interfere with functional performance.

### Implication for Future Directions

This is a very exciting time for physical rehabilitation specialist since it is evident that physical activity, particularly the acquisition of motor skills, provides the stimulus that the nervous system needs to recover. The challenge for researchers in this area is to conduct the clinical trials that will define the tasks and training parameters that result in effective therapeutic interventions. In addition, these trials must be expanded to include other populations with brain damage in order to provide greater generalizability for clinicians. The challenge for clinicians is to incorporate an evidence-based treatment approach, which integrates their individual clinical expertise with advances in neuroscience and incorporates the perspective from patients and family members. The ability to learn the necessary skills our patients need to return to meaningful and productive roles are the changes that will truly improve the quality of life for our patients with brain injury.

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# 51

## Therapy for Activities of Daily Living: Theoretical and Practical Perspectives

*Robin McNeny*

### **THERORETICAL PERSPECTIVES: FOCUS ON ADL ASSESSMENT AND INTERVENTION**

#### **Activities of Daily Living as Human Occupations**

The term “activities of daily living” was first introduced by a physical therapist in 1949 as part of a published checklist she designed to assess her patient’s performance of daily living tasks (1). Humans engage in activities of daily living in order to maintain themselves, create an outlet for self-expression, fulfill roles, and to bring meaning into their lives. Occupational therapists regard these activities as “human occupations”. As Fisher says *occupation* is the “action of seizing, taking possession of, or occupying space or time” (2). Therefore occupation is about doing and therapy directed toward resumption of occupational tasks is significant as it enables “people to perform the actions they need and want to perform so that they can engage in and ‘do’ the familiar, ordinary, goal-directed activities of every day in a manner that brings meaning and personal satisfaction” (3).

Engagement in occupation is vital to the human spirit and to health (4). Through engagement in occupation, we become competent. Engagement in occupation begins at birth and continues throughout the life span. Occupations are ordered around routines and patterns for living. Humans learn about and make adaptive responses to their world through the pursuit of occupation. Humans bring

rhythm to life as they engage in ordinary tasks through the course of days and weeks. This rhythm set within the appropriate context brings healthy balance to life. Healthy rhythm and balance includes involvement in what Adolph Meyer refers to as the “big four”: work, play, rest and sleep (5). These four areas of occupation form the core of human activity.

Assessment of and intervention for impairments in occupational performance are based on a view that clients are occupational beings. Because each person possesses an “occupational identity”, each person has a life centered on personal values, interests and roles. While values, interests and roles are abstract, occupational identity is concretely expressed through doing (6). Participation in everyday occupations develops skills, promotes competence, establishes connections with others, expands one’s sense of belonging and community while giving meaning and purpose to life (7).

Capturing the depth and meaning of ordinary daily tasks within the culture and context of an individual’s life is a central concept of occupation as a scientific guide to practice. Insight into the client’s culture and context for living are fundamental to an understanding of the client’s occupations. Because American clinicians are often entrenched in westernized middle-class culture, we have a tendency to view clients through that cultural bias (8). Modern rehabilitationists are challenged to analyze more

deeply the “whys” and “hows” behind the readily observed actions of our clients as they perform activities of daily living. Such an analysis helps the clinician understand the meaning the individual client assigns to the tasks the client chooses to do.

### Areas of Occupation

Clinicians practicing in acute rehabilitation settings usually focus on two areas of occupation: self care skills, often called personal activities of daily living (PADLs) and independent living skills, referred to as instrumental ADLs (IADLs). Occupations focused on work and play, while important, are usually addressed later in the continuum of care. PADLs include tasks commonly performed as part of a daily routine: feeding, dressing, grooming, toileting, bathing and transfers. More individual characterization and variation are found in IADLs. However, we do a disservice to our clients when we narrow the focus of the therapy program to a mere set of ADLs. Such a restricted focus minimizes the complexity and richness of occupational performance.

Brain injury interrupts life. Abruptly an individual loses his or her place in the world. Roles are disrupted. Rhythm and balance are lost. The capacity to engage in meaningful tasks is restricted. Occupational identity is shaken if not totally lost. The capacity to “do” is flawed or perhaps totally absent. Where once there was routine, now there is chaos. Where once there was satisfaction and meaning, now there is confusion. Suddenly participation in life becomes toil. In occupational therapy, the client engages in the process of “relocation of self” where skills required to resume essential life roles are taught (4).

To set the proper stage for this relocation process, the occupational therapist conducts a client-centered assessment of occupational performance. Law (7) states that each person “has unique interests and occupations through which they find satisfaction”. A client-centered assessment defines the client’s occupations while simultaneously determining how the brain injury has affected participation in valued activities. A well-conducted client-centered assessment provides the foundation for a client-centered treatment plan designed to promote occupational performance and in turn, health.

## ASSESSING OCCUPATIONAL PERFORMANCE

### Focusing the Assessment

Fisher (9) defines assessment as “a process of collecting, organizing and interpreting the relevant information that is necessary to plan and implement a meaningful, effective program of treatment”. Trombly recommends a

“top-down” evaluative approach (10) where the first stage of assessment is exploration of the client’s occupational performance issues.

Clinicians have access to a plethora of ADL assessment tools that “score” an individual’s performance on PADLs and in some cases, IADLs: the Klein-Bell Scale (11), the Barthel Index (12), the Kenny Self-Care Evaluation (13), the Assessment of Motor and Process Skills (14), the A-One Evaluation (15), the Canadian Occupational Performance Measure (16), the Allen Cognitive Test (17), Rabideau Kitchen Evaluation (18) and the Kohlman Evaluation of Living Skills (19). Table 51-1 explores some of these ADL assessment tools in greater depth.

Many clinicians employ “homemade” ADL checklists in their practices rather than using published checklists and assessments. These facility-developed evaluations are compatible with the program’s focus and mission. Many are derived from the Functional Independence Measure (20) commonly used by rehabilitation teams as a comprehensive tool for functional assessment of PADLs and IADLs.

The advantage of using a standardized and reliable tool for assessment of ADLs is the ability to retest the client’s performance over time, regardless of the testing environment. Communication between clinicians along the continuum of care is clearer when the same evaluative tool is used to assess performance. Improvements in ADL performance are apparent and reliable. However, standardized assessments often take longer to administer and to score. Though clinically important information is gained from assessments such as the AMPS and A-One, clinicians feel they lack the time to devote to such thorough, occupationally oriented evaluations.

With so many assessments available for use, clinicians must identify the goal of the ADL evaluation before selecting an assessment tool. The evaluation might have a descriptive purpose. That is, the therapist chooses to assess the client’s ADL performance at a given moment in time to describe the degree of impairment and need for therapy intervention. The evaluation could have a predictive purpose where the clinician ascertains through ADL performance the patient’s capacity to live alone, function in the community or support primary life roles. The ADL evaluation also might serve an evaluative purpose where the clinician documents progress in performance over the course of time (1, 21). Clearly some ADL assessments are better for descriptive assessment and others more appropriate for predictive assessment. Law and Letts provide a thoughtful, comprehensive comparison of 13 ADL assessments in their paper which may serve as a guide for assessment tool selection (21).

Undoubtedly, there is more to the assessment of activities of daily living than simply scoring patient’s performance using an ordinal scale. Though the scales and measures available for the rehabilitation clinician and

TABLE 51-1

ASSESSMENT	POPULATION	STANDARDIZATION	COMMENTS
Klein-Bell ADL Scale	Adults in a rehabilitation program	Good	Test-retest reliability is good; content validity is very good; lengthy evaluation to administer
Barthel Index	Adults in a rehabilitation program	Good	Test-retest reliability and content validity are excellent; lengthy to administer
Kenny Self-Care Evaluation	General adult rehabilitation	Good	Test-retest reliability poor; content validity is good; lengthy to administer
Assessment of Motor and Process Skills	A variety of populations; a school version is available and studies continue assessing the use of AMPS with different cultures	Good	Reliable and valid; can be individualized to the patient's occupations; new test items are being evaluated to expand utility of assessment
The A-One Evaluation	Adults with neurobehavioral impairment	Good	Reliable and valid however certification in the interpretation of the evaluation is recommended; can be administered during the course of routine ADLs
Canadian Occupational Performance Measure	Variety of ages and populations	Good	Reliable and valid; intended for use as an outcome measure; allows clinician to focus on client's goals
The Allen Cognitive Test	Adults with psychiatric diagnoses; some work has been done with adults with brain injury	Good	Based on Allen's Cognitive Theory, the instrument is reliable and valid but training in testing procedure and interpretation is recommended
Rabideau Kitchen Evaluation	Adults with rehabilitation diagnoses	Non-standardized	Face validity; good inter-rated reliability; provides standard way to evaluate patient performance on kitchen tasks
Kohlman Evaluation of Living Skills	Adults and adolescents, including adults with brain injury	Good	Reliable and valid; useful in determining client safety in the home/ community

\*more in-depth analysis is available in *A Critical Review of Scales of Activities of Daily Living* by Law and Letts (21).

team quantify and objectify the client's performance, a thorough assessment of ADLs requires clinicians to analyze the full spectrum of the patient's performance. The best assessment begins with an understanding of the client as an occupational being, therefore the occupational profile interview is a proper starting point.

**The Occupational Profile**

The occupational profile is a semi-structured interview conducted with the client to determine the client's roles, habits, interests, values and to confirm the client's goals for the rehabilitative process. Frequently, after a brain injury, the client is unable to reliably provide information for the occupational profile due to disorientation, cognitive deficits, language impairments or behavioral issues. In such situations, the clinician should interview family or close friends to gather this vital information.

The occupational profile promotes an understanding of the client (6). Following the interview, the clinician is able to answer the following important questions about the client:

- How does my client describe himself?
- How do my client's occupations define and maintain her identity?
- In what ways does my client's engagement in occupations allow for self-expression?
- What are my client's goals given her present disability and how do they relate to her occupations?

The occupational profile consolidates information on the client's environment, daily routine, educational achievement, social support system as well as primary areas of interest. This data defines the patient's and/ or significant other's goals for rehabilitation. These stated

goals become primary drivers for the treatment planning process yet to come.

### **Assessing Performance in Areas of Occupation**

The assessment of occupational performance involves analytically watching clients “do”, utilizing what Padilla, Barrett and Walker have identified as “mindful observation” (8). In the intensive care setting where persons with brain injury usually are dependent in ADLs, the therapist assesses the client’s PADLs while managing potential complications to minimize or eliminate the impact on later occupational performance. The OT working in the ICU monitors range of motion, muscle tone and provides splints and positioners as needed to prevent deformity and contracture. Often the occupational and physical therapists conduct co-evaluations in the ICU. As the patient improves and begins in-patient rehabilitation, the OT assesses the client’s performance of relevant PADLs. Information from the occupational profile provided by the client or family guide the performance evaluation process. Assessment begins with PADLs of greatest value and priority to the client and family. As therapy continues in day rehabilitation and outpatient therapy, the OT assessment of ADL performance is refined to focus on higher level skills to promote maximal independence in the home and community. Through the continuum of rehabilitation, occupational therapists, as “experts in occupation”, analyze the methods used by their clients to complete ADL tasks (1). The therapists discern whether observed errors are attributable to problems in range of motion, strength, coordination, balance, visual-perceptual function or executive skills and use this information to design treatment programs.

As clients transition from the hospital setting into the community, the therapist broadens the assessment of occupational performance. The home health occupational therapist has the benefit of assessing the client in his natural environment, which allows the therapist to ascertain the effects of the natural environment, culture, and support network on performance (1). Some studies suggest that assessment performed in a client’s natural environment provides the most accurate picture of ADL performance (22). Because assessment in the out-patient setting occurs in a clinical environment, the clinician must listen carefully to the client and family’s descriptions of specific ADL performance carried out at home in order to identify areas of performance breakdown or client/family concern.

Several of the evaluation tools previously mentioned comprehensively assess occupational performance, rather than just ADL skills. Use of these assessments enhances the clinician’s insight into the meaning, function and form of occupational performance for the individual client while elucidating performance components that

influence performance (6). The Canadian Occupational Performance Measure (16) assesses self-maintenance, productivity and leisure roles with an eye to those areas that the client regards as valuable and meaningful. The Assessment of Motor and Process Skills (14) guides the clinician’s observation of the client as he engages in tasks of his choice selected from an extensive list of varied occupations. During the course of task performance, the clinician identifies the motor or process skills that facilitate or impede task performance. The Arnadottir OT-ADL Neurobehavioral Evaluation (15), clinically known as the A-One, aids the clinician’s detection of potential neurobehavioral deficits that are impacting the quality of or completion of occupational task performance. Use of any of these occupationally-based assessment tools gives the clinician a fuller appreciation of the client’s occupational performance assets and impairments while promoting a more holistic and hearty assessment than that which is available through a simple ADL checklist.

### **Best Practice Methods for Assessing Occupational Performance**

The use of real versus simulated tasks during the assessment process is an important consideration. Simulated assessments lack the influence of context, which may shape, either positively or negatively, a client’s performance. Occupational performance is influenced by the context surrounding the occupation itself. Context includes physical elements such as the physical environment, the area’s topography or even the level of lighting or noise. Spiritual context involves the client’s sense of a higher being and purpose to life, both of which contribute to motivation and the inspiration to “do”. Temporal context, such as the time of year or a stage in life, have bearing on task selection and performance. A homemaker doing a cooking evaluation three days before Thanksgiving may engage with greater motivation in the preparation of apple pies for her family dinner than she would in the preparation of a soup-and-sandwich lunch for herself using a menu planned by her therapist (23). Context is an inescapable part of the assessment process.

Simulated activities as a form of assessment, while not ideal, are necessary in many clinical settings. Clinicians working in hospitals may employ several strategies to improve the quality of simulated assessments. Through interviews, clinicians may obtain detailed information about the client’s home environment and insert as many of these features as possible into the assessment. For example, the therapist might learn that the client’s bedroom contains a low chair routinely used for dressing. During the dressing assessment, the clinician utilizes a chair of the same height to determine the effect of sitting

on a lower surface during dressing. Some OT kitchens have moveable islands that allow therapists to configure the kitchen as similarly as possible to the client’s home. If the patient plans to use a regular bed at home, the therapist should perform all bed-related assessments with the hospital bed flat and the rails down. Real coins and bills improve the quality of money management skills assessment. Provision of the client’s own grooming tools and supplies in the bag or container used at home enhances the physical context of the task.

**Assessing Client Factors that Affect Performance**

At times, therapists find it necessary to assess specific components of functional performance further to identify the nature of or severity of an underlying problem. Known as client factors, these components are peculiar to the individual client and play a role in the client’s ability to perform functional tasks. Client factors include mental functions, sensory functions, neuromusculoskeletal and movement-related functions, visual and speech functions. Table 51-2 provides some examples of client factors (23). Perhaps the therapist notices while assessing bathing that the client cannot reach her lower back. A specific evaluation of the client’s upper extremity range of motion and strength reveals that though her shoulder range of motion is within normal limits, her antigravity strength is insufficient to support washing her lower back. In another case, during an assessment of a client’s self-feeding skills, the clinician notices that the client over-reaches for her milk carton, closes one eye when scooping food with her fork and sometimes closes both eyes when chewing. A quick assessment of ocular alignment reveals a diplopia that is interfering with the client’s comfort and precision during PADL’s.

Formal testing of client factors, such as visual-perceptual or memory assessments, is based upon an assumption that there is a relationship between the factor being tested and the client’s ability to perform the daily living task (9). Tests such as the Toggia Cognitive Assessment (TCA) (24), the Lowenstein Occupational Therapy Cognitive Assessment (25) and the Contextual Memory Test (26) are used to assess client factors. Researchers continue to seek evidence of a correlation between tests such as these and occupational performance (27).

The complete occupational performance assessment provides a picture of the client’s occupations within context, an understanding of the client’s and/or significant other’s goals for the therapy process as well as information on impairments in client factors that limit overall performance. Armed with a good assessment, the clinician proceeds to plan treatment to promote the client’s relocation of self, all the while keeping the client’s priorities and goals for the treatment process in mind.

**GOAL SETTING STRATEGIES**

In times past, health care providers paternalistically offered advice and treatment to clients to remediate their conditions or symptoms. This advice and the prescribed intervention was offered with the client’s best interests in mind. In most cases, clients accepted the health care provider’s advice and treatment without question, believing that the health care provider knew best. Whatever priorities the health care provider set were “fine”– even if they didn’t match the client’s own priorities.

Times have changed. Now individuals receiving medical services are more informed, more involved in decision-making and more vocal about their preferences. Client-centered goal setting is now routine in many health care settings. Major health care accrediting agencies, such as JCAHO and CARE, require evidence of the client’s and significant others’ input into the goal-setting process. Current research demonstrates that client-identified goals yield the best therapy outcomes. Therefore, goal setting with the client and caregiver is an integral part of the rehabilitative process. Often goals identified by clients and especially by caregivers focus on areas which, if improved, make return to home and care in the home easier. Those clients who initially are unable to state their rehabilitation goals must be given the chance to provide input once able (28). At times, clients set lofty long-term goals, such as driving, returning to school or work or staying home alone. In such situations, the clinician works with the client to outline realistic and attainable short-term goals, never losing sight of the client’s long-term goals.

Once ADL-related treatment goals are set, intervention focuses on the client’s ability “to do” (29). A well-defined treatment goal integrates the client’s expressed

**TABLE 51-2**  
*Examples of Client Factors*

Mental functions	Level of arousal, orientation, personality, motivation, attention, visual-perceptual function, judgment, mathematical calculations, motor planning
Sensory functions	visual acuity, hearing, balance, taste, smell, tactile discrimination, pain
Neuromusculoskeletal and movement-related functions	range of motion, mobility, strength, muscle tone, reflexive responses, eye-hand coordination, tics and tremors, ability to ambulate
Skin and related structure functions	skin integrity including the presence of wounds



**TABLE 51-3**  
**Examples of Goal with Qualifiers**

<p>Patient will place arms in sleeves of shirt with moderate assist while sitting in wheelchair.</p> <p>Patient will calculate money up to \$2.00 in coins with 40% accuracy.</p> <p>Patient will bring washcloth to face with maximal assistance.</p> <p>Patient will prepare shopping list for a simple breakfast using a planned menu, with minimal assist.</p> <p>Patient will complete entire morning grooming routine in 30 minutes with supervision.</p> <p>Each of these areas of consideration are important and should be kept in mind during the treatment process.</p>
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skills and desires with the environmental context in which the client functions. The treatment program includes tasks, activities, and instruction to meet these goals. As Baum et al. says so well: “The unique contribution of occupational therapy is to maximize the fit between what the person wants and needs to do and his or her capability to do it” (1).

Well-formulated treatment goals are functional, measurable, specific, clear to the reader and reflective of the client’s priorities. Achievement of treatment objectives is easily determined when goals are written well. Goal qualifiers enhance both the specificity and the achievability of treatment goals. Goal qualifiers may include quantifiable measures such as the frequency with which a task is performed, the rate of accuracy achieved during performance, the setting in which a task is performed, or the number of rest breaks required during task performance. Table 51-3 lists several different types of goal qualifiers.

As treatment goals are achieved, the clinician in collaboration with the client sets new functional goals. New areas of occupational performance are introduced into the treatment program as the client demonstrates readiness for engagement in advanced tasks. Good communication between clinicians about goal achievement and the client’s goal priorities as the client progresses through the continuum of care facilitates progression of the treatment plan.

The clinician may employ one of several strategies to solicit client involvement in the goal setting and goal progression process. Team conferences that include clients and families provide a forum for the entire team to review progress and establish treatment priorities. A review of treatment goals by clinicians at the beginning of each treatment session gives the treatment session focus. Memory notebooks may include a section devoted to mapping treatment goals. One recent study recommended the use of a “goal notebook” to improve clinician-client discussions and to remind both the client and the clinician about active treatment goals (30).

## ADL INTERVENTION: BRINGING MEANING BACK TO LIFE

### Improving Personal Activities of Daily Living

Personal activities of daily living (PADL) include bathing, bowel and bladder management, dressing, eating, hygiene and grooming and functional mobility (23). Each person performs PADL’s in personally unique and individually customized sequences. Clients with severe brain injury frequently experience limits on their ability to perform these most basic and familiar tasks (31). Many factors contribute to deficits in self-care performance, including impaired function of the upper and lower extremities, cognitive deficits, visual-perceptual impairments, communication impairments and behavioral problems.

The comprehensive PADL treatment program provides retraining opportunities that incorporate multiple considerations associated with PADL performance. These parameters include:

1. the *context* in which the tasks are performed
2. the client’s *habits and routines* related to task performance
3. *safety* during performance of tasks
4. the efficacy of *adaptive devices and compensatory techniques*
5. *interdisciplinary team involvement*, including the caregivers
6. the client’s ability to *self-monitor and correct errors*

Knowledge of *context* related to PADL’s performance is critical. Cultural context influences the client’s choice of attire, food choices and grooming preferences. Knowledge of the physical context in which PADL’s are performed helps the clinician design strategies to overcome architectural barriers, such as inaccessible bathrooms or out-of-reach clothes closets. An awareness of context helps eliminate the imposition of the therapist’s values on the client. For example, the therapist might insist during treatment that the client place the dinner napkin in his lap during meals only to discover that the client and his family always keep napkins, as well as their elbows, on the table during meals. Treatment programs must be contextually relevant or they are ultimately of little value to the client.

PADL’s are habit-driven. *Habits* are “automatic behavior that is integrated into more complex patterns” which facilitate daily performance of self-care (23). PADL’s are so habitual that most people proceed through morning and evening self-care tasks without much conscious thought. It is helpful to the retraining program to know the client’s pre-injury habits (32). Knowledge of pre-injury habits helps the clinician formulate a treatment program that draws upon familiar patterns of behavior

that may hasten skill competence. Did the client put socks on before or after trousers? Did the client shower in the morning or evening? Was moisturizer used under makeup? Sometimes clients serve as the source of this information. However, if the client cannot provide information regarding pre-injury habits, the clinician needs to obtain this information from families. Unfortunately, because many PADLs are performed privately, families may have limited insight into the client's pre-injury habits.

The motor, cognitive, behavior and visual-perceptual sequelae common after brain injury often make performance of some PADLs risky. *Safety* is a primary concern for the clinician. Clients with dysphagia require assistance or supervision for self-feeding. Clients with balance problems may not be able to safely stand during self-dressing. Problems with incoordination, muscle weakness or visual-perceptual function can make shaving or the application of eye make-up hazardous. In addition, the unpredictability associated with impulsivity creates an environment wrought with potential safety risks. A portion of the treatment regimen must be devoted to training in the integration of safety-enhancing strategies. The therapist might advise that dressing be performed in supine in bed or that the client use an electric razor instead of a straight razor. Caregiver instruction should include training in safety concerns as well as the admonition to expect the unexpected, especially if the client has impaired self-awareness, demonstrates impulsivity, has apraxia or is confused.

*Adaptive devices* may prove helpful when motor impairments interfere with task performance. However, when memory impairments are marked, clients often forget that they have adaptive devices and thus, fail to use them. Clients who utilize elastic shoelaces may proceed to untie their shoes when undressing. Apraxia may impede the client's ability to learn to operate an adaptive device, provoking the client to abandon its use in frustration. Clients experiencing disorganization and poor sequencing may lose track of adaptive devices or fail to have them handy at the critical moment. Clinicians should consider carefully the real benefit of adaptive aids to clients with brain injury. Likewise care should be taken when devoting precious treatment time to training in the use of adaptive devices.

Clients with brain injury frequently must learn to do familiar tasks in a new ways. The use of *compensatory strategies* during PADL performance is often successful. Compensatory strategies address areas of performance breakdown. The clinician performs task analysis to identify elements critical to task performance. Task analysis involves in-depth study of the physical, cognitive and behavioral requirements of a given activity. Task analysis is applicable to any occupation, from the simplest of self-care tasks to work-related tasks. A comparison of the task requirements with the client's abilities and limitations reveals the points in task performance where

compensation or adaptation must occur to facilitate successful performance.

When teaching compensatory strategies, the clinician first structures the task, adding new elements to address the areas of breakdown. Clients unable to maintain standing need to learn to dress and bathe in a sitting or supine position. Clients with homonymous hemianopsia must learn to purposefully look to their "blind side" during feeding, grooming and dressing. Clients with severe sequencing deficits may require a written checklist to complete their morning PADL routine. A client with tonal dysfunction that worsens during strenuous activity may need a tone-reducing orthosis during ADLs. With the therapist close at hand, the client proceeds through the PADLs incorporating compensatory strategies while receiving either verbal and/or physical assistance as needed.

Once the PADLs are structured, the client practices task performance to facilitate learning. Chunking instruction in compensatory techniques may reduce the chance of overwhelming the client (32). The chunking strategy may be used, for example when addressing impairments in self-dressing with a client with hemiplegia. The therapist first teaches a compensatory technique for upper extremity dressing. The upper extremity dressing technique is practiced daily with the therapist providing assistance with lower extremity dressing. Once the client masters the upper extremity dressing technique, treatment progresses to lower extremity dressing. A compensatory strategy to facilitate independence with lower extremity dressing is taught by the therapist. Therapy focuses on practice of lower extremity dressing strategies with the therapist providing physical and verbal assistance. Once the client demonstrates competence with the two parts of dressing separately, the dressing sequence is put together and practiced until mastered.

Chaining and prompting techniques are used to facilitate learning of compensatory strategies. Because functional tasks are comprised of sequences of steps, retraining of task performance may be accomplished by forward, backward or whole-task chaining. Forward chaining involves teaching the first task step first, adding subsequent steps as the client is ready. Backward chaining entails teaching the final step task first, such as teaching a client to put on and tie his shoes first before other garments are taught. Once the last task step is mastered, the clinician works backward toward the first step of the task as the client demonstrates readiness to learn. Whole-task chaining, which proved most successful in a study by Giles, presents all task steps in their proper sequence coupled with repeated practice until competence is demonstrated (33).

Chaining allows the client to use completed steps as cues to initiate subsequent steps. Therapists either verbally assist the client through the chain of steps or provide written cue cards that outline the task sequence.

When the client is unable to move on to the next step, the therapist may query the client. Questions such as “You’ve put sugar in your coffee. What do you do next?” or “You’ve finished washing your face. What comes next?” often triggers the client’s recall of the next step or his need to reference his cue card. As the client’s competence with the task improves, fewer cueing queries from the clinician are required.

Though the area of PADL is typically the domain of the occupational therapist, the entire *interdisciplinary team* including the caregiver must be involved in the PADL treatment process. Performance of PADL’s occurs throughout the 24-hour day necessitating the participation of nurses, other therapy staff, residential staff, caregivers and family to ensure carryover of newly learned techniques, to provide consistency in cueing, to ensure safety and to promote learning thus increasing proficiency. Communication among the interdisciplinary team members regarding PADL performance must occur routinely. In-patient programs often rely on boards posted at clients’ bedsides upon which clinicians record self care performance information. Memory diaries that document PADL performance and strategies are used in in-patient programs, outpatient programs and in the community. Videos of clients performing self-care help clarify levels of performance and provide instruction for distant caregivers. Team meetings provide an opportunity to discuss self-care performance. Communication is fundamental to providing the consistency that is essential in all areas of brain injury rehabilitation.

Throughout the retraining process, the client must be taught to *monitor performance for errors* and to initiate self-correction. Feedback is one method for teaching error recognition. Feedback may involve the clinician showing a client mistakes made during task performance. While this approach works, the clinician or another individual is essential to such a feedback process.

A better technique involves guiding the client through a sequence of activity prediction, self-critique and problem solving. In activity prediction, the client estimates how he will do on a given task before the task commences. Using information from prior performances, the client identifies areas where breakdown might occur. Once the client completes the task, the client engages in self-critique, comparing actual performance with predicted performance. Activity prediction followed by self-critique improves the client’s self-awareness and improves performance (34).

Some clients repeatedly commit the same errors, at times due to an inability to approach a task in a novel, potentially more successful manner. One approach to reduce repeated errors is to help the client generate alternative approaches to a task. When a therapist notes that an error is occurring repeatedly, the therapist should work

with the client to identify areas of performance breakdown noticed during task performance. Some clients are able to identify errors spontaneously but others require the assistance of the therapist to review each step of the task. Once the pattern of error is identified, the clinician guides the client through an analysis of possible alternatives to task performance that could eliminate the repeated errors. The alternatives are then employed during task performance and analyzed by the client and therapist. Those that prove beneficial to the quality of performance are incorporated into the task routine.

### **Interventions for Deficits in Instrumental Activities of Daily Living**

Instrumental activities of daily living (IADL’s) are those activities “oriented toward interacting with the environment” and are often multifaceted in nature (23). Completion of IADL’s is usually essential to an individual’s capacity to live independently in the community. In some cases, family members may rely upon the individual to complete specific IADL’s to keep the family unit running. IADL’s include activities such as caring for other humans or pets, use of communication equipment, community-based mobility, home management, providing food for self and perhaps others and managing finances.

Because IADL’s are so complex, they are very susceptible to significant disruption after brain injury. Physical limitations such as hemiplegia, impaired balance and incoordination impact IADL’s that require bilateral extremity use to complete, such as folding laundry as well as activities that entail precision, such as dialing a cell phone or chopping vegetables for a salad. The complexity of IADL’s places a high demand on cognitive function, including memory function, executive skills, reasoning, judgment and problem-solving. Visual-perceptual-motor dysfunction such as impaired spatial skills, apraxia and hemi-inattention make accurate, independent performance of many IADL’s very difficult, if not impossible. Functional communication, money management and home management depend to some degree on language function.

Each person possesses a unique repertoire of IADL’s. Valued IADL’s are related to a person’s life roles such as parent, home maintainer, worker, student, or volunteer. Competency requirements for specific roles vary from person to person.

There is no “cook book” of interventions for treatment of dysfunction in IADL’s though treatment-oriented resources are available to the clinician (8, 22, 31, 35–39). Limited research into the effectiveness of some therapeutic approaches has been done (19, 22, 28, 36, 37, 40–44). The optimal intervention for disruption in IADL performance is personalized for each client based on the client’s preferences, willingness to adapt task performance, the

nature of the task itself and the impact of the sequelae of brain injury on task performance.

During treatment planning, the clinician should be mindful of several important points. Though the approach, strategies and techniques employed to provide intervention for IADLs vary with each patient, these considerations supply a guide for the treatment planning and implementation process.

1. the *client and family's goals* relative to previously performed IADL
2. the *setting* in which treatment for IADLs is occurring
3. facilitation of *generalization of skills* learned
4. selection of *treatment tasks*
5. utility of *technology* during task performance
6. *educational needs* of the client and family

The over-riding goal of rehabilitation is to enable the person receiving care to attain a satisfying quality of life. Disturbing data exists regarding quality of life after brain injury. In one study, at follow-up, a small proportion of patients was competitively employed. Of those studied, 12% rarely left their home because of continuing functional limitations (41). While each person defines "quality of life" differently, it is imperative that the *clients and their significant others' goals for rehabilitation and perception of quality within their own lives* form the foundation for treatment. Some families tolerate role changes within the family system better than others. While one husband is perfectly comfortable assuming all the responsibilities of home management given his wife's disability, another husband may regard his wife's ability to manage laundry, prepare meals and do housework to the extent she is able as a vital necessity to the family. Many family units need the client to be able to stay alone for a period of time during the day in order for family members to work or attend school. In such cases, the therapist must address the numerous activities essential to that client's safety and independence while home alone. In addition, clients often state a desire to resume tasks that bring special meaning to life, such as participation in religious worship or participation in the weekly bridge club. Therapists who listen carefully to their clients are able to determine the client's treatment priorities.

Once treatment priorities are identified, the therapist begins the intervention process. Clinicians must not underestimate the power of client investment on the outcome of treatment. As Pierce articulately states: "The appeal of a therapeutic activity, and thus, its treatment power, always depends on the degree to which the patient perceives it as offering desirable levels of pleasure, productivity and restoration" (45).

The *setting* in which IADL treatment naturally occurs influences the types of activities used in remediation and the nature of the treatment itself. Without question, a

familiar environment enhances performance because well-known task elements serve as prompts for the client. In fact, some researchers have concluded that treatment in an unfamiliar environment is fraught with distraction and thus is a hindrance to the client (22).

Despite shortening lengths of stay, in-patient treatment programs often begin the IADL treatment program. The in-patient therapist is challenged to provide the most realistic treatment environment possible within the hospital setting. Some in-patient rehabilitation programs feature Easy Street<sup>1</sup>, a mock naturalistic environment that includes a retail shopping area. Though not equivalent to working with the client in the "real world", mock environments like Easy Street or even the hospital gift shop and eateries enhance context. Functional tasks such as ordering from a menu, handling money, following directional signs, use of public restrooms and managing architectural barriers may be practiced in such environments. At least one paper reports a longer length of stay and less favorable FIM scores for patients who received treatment only in a clinic setting as compared to patients who had at least one session in the Easy Street environment (46). In-patient settings without benefit of the Easy Street environment may enhance contextual relevance by using the client's own recipes during cooking tasks or working on financial management using copies of the client's bills. A collection of phone directories from surrounding regions for use during phone skills retraining improves familiarity. Community outings to grocery stores, shopping centers, and restaurants formerly frequented by the client provide excellent environments for therapy. Use of more natural and contextually relevant therapeutic media within the clinical setting is recommended. The standard collection of pegs and cones can be replaced with functional task modules such as car maintenance kits, pet care supplies, a set of greeting cards to practice writing skills and coupons for sorting (36, 37). In an age where provider productivity and efficiency are mandated within the clinical setting, greater creativity is required of the clinician who desires to provide maximally relevant treatment to clients. The extra effort though is worth it when contextual relevance is improved.

Much IADL treatment occurs in outpatient, day rehabilitation and home settings as clinicians work with clients who are actively re-integrating into their naturalistic environment. Outpatient and day rehabilitation efforts may be augmented by "homework" assigned by the clinician and performed between clinical appointments. The home health therapist has the real benefit of engaging the patient in IADL retraining in the most familiar environment.

<sup>1</sup>*Product Information* Easy Street – Exclusively manufactured, sold and installed by Chamberlain West, Inc, 7300 E. Acoma Drive, Scottsdale, Arizona 85260

As the treatment program progresses, the clinician must be concerned about the client's ability to *generalize into the natural environment the skills being mastered* in the treatment session. Generalization involves the client's ability to do as well in the home setting as in the clinical setting. Cases have been reported where clients do less well when the clinician or the clinical setting are withdrawn from the context of the activity (22, 42). Neistadt emphasizes that clients with brain injury often depend on a "data-driven mode of information processing" during pursuit of IADLs. Such behavior causes inflexibility in thinking, demonstration of stimulus-bound behavior and failure to generalize (42). Techniques developed by Toglia (34, 38) and Ben-Yishay (22) create a therapeutic environment where cues and assistance are provided but gradually faded as performance progresses. Neistadt describes application of these strategies to food preparation tasks (42). Maximization of generalization is achieved by providing opportunities for practice in as many contexts as possible. Inclusion of family in the treatment session provides one alteration to task context. Practice of tasks either in a transitional apartment, while on pass or in the home between outpatient sessions provides variation in contexts. In some situations, generalization simply doesn't occur. In those situations, therapists should shift the treatment program to the practice of specific tasks in specific contexts to gain the highest level of performance competence.

When planning treatment for IADLs, the clinician should weigh the client's *choices of treatment tasks* carefully as well as the appropriate approach to treatment. All IADLs may be therapeutically graded to provide a suitable level of challenge. Grading techniques involve changing specific task parameters such as tools needed for task completion, the amount of environmental distraction, the complexity of the task and the amount of cueing offered by another person. Treatment always begins at a level where clients are challenged but not frustrated. The selection of treatment activity is guided by the client's stated goal and should be an activity in which the client has expressed interest. As performance improves, the elements of the treatment task are advanced to more greatly challenge the patient.

An occupational therapist treating a client with topographical disorientation, right-left confusion and hemi-inattention focuses the treatment plan on the client's expressed interest in meal planning. The client clips coupons to help reduce her food costs. One treatment modality employed to address the hemi-inattention and right-left confusion could be sorting coupons for food products to the left and cleaning products to the right. The OT might introduce map reading as a therapy activity. The therapist orients the patient to the map, incorporating directional terms. The complexity of the maps used increases as the client shows improved map reading

skills. Once improvements in right-left sorting and map reading tasks are noted, therapy progresses past the confines of the OT clinic into the medical facility. The OT provides written directions for a route from the OT clinic to the facility's front door. As part of the treatment session, the client uses the written directions to travel to the prescribed route. The written directions contain landmarks on the right and left that the client must note along the way. In addition to in-clinic therapy, the OT provides a homework assignment requiring the client to use written directions to find the OT clinic on the next visit, asking for assistance as needed. As treatment progresses and improvements are noted, the clinical treatment program and homework assignments are made more difficult. Advanced treatment could include having the client read directions to the person who provides transportation to OT appointments, training with the OT in the use of public transportation or the use of a state map to plan a vacation. Clinicians must make deliberate treatment modality selections based on the client's occupations and then progress the task complexity as the patient demonstrates readiness.

Ever-evolving *technology* has great potential for many clients with brain injury. Staying current with technological advances is a challenge for busy therapists and funding assistive technology is often difficult, if not impossible, for many individuals with brain injury. However, technology does provide some tremendous possibilities. Low-tech devices available at modest cost allow clients with severe motoric impairments to control their environment, such as turning on lights and using the telephone. Computers provide voice-activated options as well as adaptive peripherals which facilitate word processing for individuals without hand function (47). Electronic aids to daily living (EADLs) dial telephones, unlock doors and provide many options for environmental control.

Cognitive orthotics, sometimes called assistive technology devices (ATD's), provide "support for weakened or ineffective brain functions" (43). Such orthoses provide cues, assist with task completion, maximize self-management, allow a higher level of self-sufficiency and often promote self-esteem and self-confidence (43, 44, 48). Individuals without brain injury employ cognitive orthoses such as portable digital assistants (PDA's), portable tape recorders, watch alarms and computer-based schedulers routinely. The ISAAC cognitive prosthetic system has shown great promise in assisting clients with brain injury. A recent report (49) demonstrates the utility of this small device. Its advantages over other cognitive prosthetics include its compact size, portability, its adaptability to the individual client's needs, and its immense programming possibilities. Cognitive prosthetics have shown utility with clients with brain injury (48) and have the added advantage of being a tool used by people without disability, unlike traditional memory notebooks.

As clinicians seek technological solutions for their clients, several factors must be kept in mind. First, the client's desire to employ a technological solution must be explored. The therapist needs to determine the client's overall awareness of his deficits and how technology, when properly employed, may help. The therapist must conduct a task analysis of the client's remaining abilities and strengths that could support use of technology while also considering the intactness of client factors often essential to technological use, such as vision, language skills, ability to keep up with the device and the ability to manipulate the device (48). The cost of technology also needs to be considered. Care must be taken when introducing potentially life-changing technology to a client who lacks the financial means to purchase the device. Alternative funding sources, such as vocational rehabilitation services or even charitable organizations, are sometimes available. The motivated client can partner with a clinician to look for alternate funding. Finally, the clinician should consider the client's overall familiarity with technological devices. A client with an information technology or engineering background may more quickly learn how to use an IADL than a client who has never used a computer and who has no mechanical background. Technology has awesome potential to assist individuals with brain injury manage IADLs despite their physical or cognitive sequelae.

Throughout the IADL treatment process, clinicians must remain alert to the *educational needs of the client and family*. It is difficult for clinicians to imagine or anticipate the many issues and concerns of the caregiver, especially if the clinician has never provided personal support for a person with a brain injury. Understanding the complexity of brain injury is not easy for clients or for families. During the treatment process, families may wonder why their loved one doesn't do the things that he is perfectly capable of performing. For example, a wife may say to the therapist: "I saw my husband fix his own lunch with you. Why is it when I come home from work I discover that he hasn't gotten off the couch all day. Why doesn't he fix his own lunch at home?" Clients may wonder why they never seem to be able to finish any task they start. Education about the significant impact of impaired executive function is usually helpful for families and clients who may have received considerable instruction on performance of transfers, the administration of medications and home exercises but who have not learned sufficiently about perseveration, impaired initiation and decreased planning. As stated by McDonald et al. (50): "Impairment in executive abilities has significant implications for the day-to-day life of those who have sustained traumatic brain injury" – implications that families and clients don't always understand.

Clients and families also benefit from intense instruction in safety related to performance of IADLs. Clear advice regarding supervision needs, use of dangerous

implements such as power tools and the operation of motor vehicles must be given. Families need guidance on activities the client may safely and capably do alone, whether in the home or in the community. Discussions regarding the client's degree of self-awareness may be relevant. Lack of awareness is a common sequelae of brain injury and can lead to all manner of difficulties including resistance to rehabilitative efforts, deliberate involvement in unsafe activities and interpersonal conflict (51). As intervention is employed to improve the client's self-awareness, support and education for the caregivers may foster their ability to carry on and cope.

Families will often ask whether the client can do particular IADLs that the therapist has not yet addressed clinically. Clinicians must take care when basing judgments about a client's ability to perform tasks at home and in the community on testing of component skills or on simulated activities. For example, a therapist might state that a client is unable to stay home alone because the client performed poorly on a visual-perceptual test. While some component testing has shown encouraging relationships to IADL performance, there clearly is a disconnection between performance on a paper-pencil task related to an IADL and performance of IADL itself (22, 27). Likewise, asserting that a client is incapable of certain IADLs based on a simulated task is a stretch. Clinicians may offer predictions based on an analysis of performance components and results of simulated activities, but with caution. The best approach is to engage the client in the task in question to determine the client's actual skill level. Otherwise clinicians find themselves stating their best guess based on previous experience and the data at hand.

Clinicians do well to maintain an open door for clients and families to ask questions and receive education, not only during active treatment but also after formal treatment has ended. Improvements in as well as deterioration of IADL performance occur long after the therapy program ends. The desire and need for therapy also changes over time. One study reports that some survivors of brain injury sense a greater readiness for therapy long after the course of therapy is completed (41). Clients and families need to understand what is "expected" and "normal" after a brain injury and what constitutes a situation of concern. Referring clients and caregivers to brain injury support groups may provide a valuable resource over time.

## OCCUPATIONAL THERAPY IN BRAIN INJURY REHABILITATION

The occupational therapist functions as a part of the interdisciplinary brain injury team. Occupational therapists are trained to view clients holistically as occupational beings for whom participation in daily life is a vital part

of existence. Occupational therapists seek to improve the health of those receiving occupational therapy services while engaging clients in meaningful activity. The best occupational therapy utilizes treatment modalities that inspire and motivate the client while providing relevant experience.

Occupational therapy educational coursework includes basic sciences, anatomy, physiology, neuroanatomy, kinesiology as well as instruction in disease and disability. In addition, occupational therapy students study psychology, sociology and human development. The language of occupational therapy theory and practice is found in the *Occupational Therapy Practice Framework* that describes the domain and process of occupational therapy (23).

Occupational therapists who practice in brain injury rehabilitation programs benefit from continuing education focused on cognitive function, behavior management and intervention techniques. While the occupational therapy educational curriculum provides a basic foundation in these areas, further education sharpens the clinician's skills. The ever-evolving field of assistive technology demands that the occupational therapist continually review the literature for developments applicable to persons with brain injury.

The most significant contribution of the occupational therapist to the brain injury rehabilitation team is the therapist's understanding of and insight into the individual client's ability to participate in activities of daily living of interest and importance to the client and the family. The occupational therapist's ability to analyze task performance is critical to the team's understanding of the client's need for assistance and supervision in the community. Occupational therapists are not "ADL retrainers". Rather occupational therapists alter context during treatment in order to clarify important issues in functional task performance for the client, family and treatment team while facilitating maximal participation in activities of importance to the client.

Utilizing a collaborative approach, the physician and occupational therapist do well to mesh their understanding of the client's participation in daily life prior to the brain injury with the client's and family's stated rehabilitation goals. While a full restoration to pre-injury participation isn't always possible, the physician and OT must work with the client and family to establish reasonable, achievable expectations for improvement and performance. The physician should encourage the occupational therapy staff to be creative and innovative in treating patients. The occupational therapist and physician should work together in setting parameters on client activity, especially in the areas of driving, return to work and living situation based on the therapist's evaluation and intervention with the client in a variety of tasks and

contexts and the physician's knowledge of the client's medical condition.

## CONCLUSION

Law states (7) that "participation in the everyday occupations of life is a vital part of human development and lived experience". Brain injury can radically affect an individual's level of participation in everyday activities. Reduced participation in important life tasks affects the client's sense of competency within the environment as well as overall satisfaction with life. Therapeutic efforts directed toward improved participation in occupations must be uniquely designed to capture the client's interest as together the client and clinician work toward the client's return to quality of life and relocation of self.

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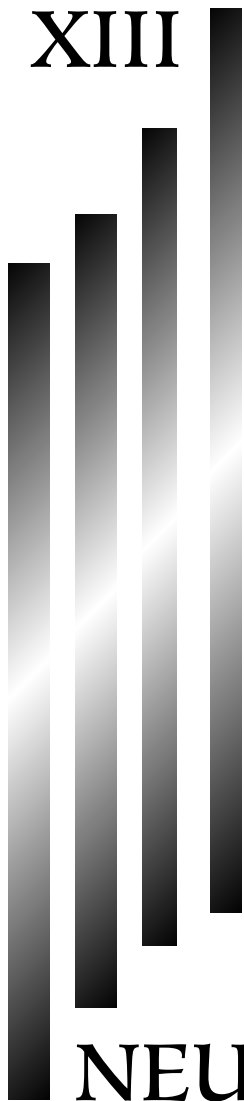
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XIII



NEUROPSYCHO-  
PHARMACOLOGY AND  
ALTERNATIVE TREATMENTS

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# 52

## Pharmacotherapy of Neuropsychiatric Disturbances

*Jonathan M. Silver*  
*David B. Arciniegas*

### INTRODUCTION

The neuropsychiatric consequences of traumatic brain injury (TBI) are many and varied, but include problems such as depression, mania, affective lability, anxiety, apathy, psychosis, aggression, fatigue, and sleep disturbances, among others. Each of these conditions may occur as an independent problem following TBI, but often occur in combinations or partial forms that cross conventional diagnostic boundaries. These conditions most likely arise as a combination of pre-injury vulnerability factors (including pre-injury psychiatric problems, genetic issues, and psychosocial circumstances, etc.) and injury-related factors (location and/or severity of injury). Additionally, the development and persistence of such problems is often complicated by a host of post-injury factors including psychological responses, coping styles, social and economic circumstances, and medicolegal issues. The relationships between pre-injury, injury-related, and post-injury factors as they contribute to posttraumatic neuropsychiatric disturbances are complex (see Figure 52-1). Consequently, the task of understanding the development of neuropsychiatric problems in persons with TBI is necessarily a complex one. A complete review of these issues is beyond the scope of this chapter, and these problems are addressed in considerable detail elsewhere in this volume. Although we will offer some discussion of the most common posttraumatic neuropsychiatric disturbances in the

context of reviewing their pharmacologic treatments, clinicians should be mindful that these therapies should be prescribed only after a thorough and neuropsychiatrically-informed evaluation of each person for whom they are prescribed.

Regardless of the mechanisms by which they develop, the neuropsychiatric consequences of TBI complicate neurorehabilitative efforts and are a substantial source of suffering for those in who they develop. There are at present a host of therapeutic options for the neuropsychiatric consequences of TBI, including both non-pharmacologic and environmental interventions as well as pharmacotherapies. Similar to the treatment of psychiatric disorders such as depression, panic disorder, and obsessive-compulsive disorder, a combination of therapeutic interventions (e.g., medications, rehabilitative therapies, psychotherapies) administered simultaneously to the person with neuropsychiatric disturbances after TBI is often more effective than is treatment using only one of these modes of treatment. Individual, cognitive, behavioral, and family therapy, as well as environmental accommodations, may alleviate neuropsychiatric disturbances and improve recovery from and/or adjustment to TBI. Nonpharmacologic interventions are not addressed in the present chapter, but are instead reviewed in Chapter(s) elsewhere in this book. In the present chapter, we review the pharmacotherapy of these neuropsychiatric disturbances following TBI.

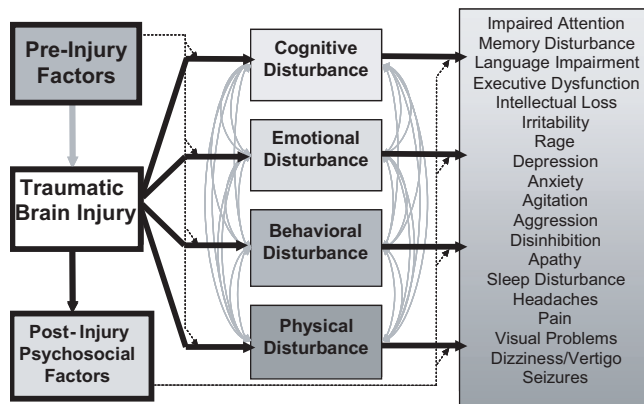


FIGURE 52-1

A schematic diagram of the complex interactions between pre-injury, injury-related, and post-injury factors that contribute to the development of neuropsychiatric disturbances following traumatic brain injury. The column on the left depicts each of the major contributing factors to neuropsychiatric outcome. Pre-injury factors such as impulsivity, risk-taking behaviour, and substance abuse may contribute to the occurrence of TBI. Depending on the location and severity of injury to the brain, cognitive, emotional, behavioral, and physical disturbances may arise from direct injury to brain structures serving each of these domains of neuropsychiatric function (middle column). Pre-injury variables such as baseline cognitive function, medical, neurological psychiatric, and/or substance use disorders may modify the effects of injury on each of these domains. After injury, symptoms in one domain may affect symptoms in one or more of the others (e.g., pain symptoms worsening attention, producing irritability, and contributing to agitation; depression worsening cognition, producing apathy, and increasing perceived severity of headache, dizziness, and other physical postconcussive symptoms; etc.). Problems in each domain of function contribute to presenting symptoms (partial list, far right). Post-injury factors such as social support, treatment and other rehabilitative interventions, socioeconomic status, and medicolegal issues may influence the expression, persistence, or remission of neuropsychiatric symptoms. Understanding the complex interactions that contribute to these symptoms informs the evaluation, diagnosis, and treatment of neuropsychiatric disturbances following TBI

### EVALUATION

For purposes of this discussion, we will assume that prior to initiating any pharmacologic treatment the treating clinician has completed a thorough psychiatric, developmental, and neurological history and examination. When considering the prescription of medications for posttraumatic neuropsychiatric symptoms, two issues require additional attention. First, the presenting complaints must be carefully assessed, defined, and operationalized, preferably through the use of objective rating scales such as the Neurobehavioral Rating Scale-revised (1, 2) or the

Neuropsychiatric Inventory (3), or more symptom-specific scales such as the Overt Aggression Scale (4) or Apathy Evaluation Scale (5). In addition to clarifying the type, frequency, and severity of symptoms prior to treatment, repeated use of such scales during treatment improves the accuracy and objectivity of monitoring treatment responses (both beneficial and adverse).

Second, the use and effectiveness of all ongoing treatments must be reevaluated, including pharmacologic and non-pharmacologic therapies, whether these are prescribed or self-administered. When reviewing the patient's current medication regimen, three key issues should be addressed: 1) the indications for all drugs prescribed, 2) whether currently prescribed medications are still necessary, and 3) the potential side effects of these medications. Patients who have had severe brain trauma may be receiving many medications that either result in or exacerbate psychiatric symptoms such as depression, mania, hallucinations, insomnia, nightmares, cognitive impairments, restlessness, paranoia, or aggression. Consultation with other treating clinicians may be required to decide whether a presently prescribed medication is necessary and/or whether a new medication might be helpful. Sometimes such treatments have not been properly applied, are predicated on misdiagnosis of the problem, or are the result of poor communication among treating professionals regarding the problem in question. In some cases, a potentially effective medication has not been beneficial because it has been prescribed in a dose that is too low and/or for a period of time that is too brief. In other instances, the most appropriate pharmacological recommendation is to eliminate some ongoing treatments. After a thorough assessment of both target symptoms and their treatments, the most useful recommendation will sometimes be to offer no medication at all and instead to use nonpharmacologic therapies.

### GENERAL PRINCIPLES OF PHARMACOLOGICAL TREATMENT OF PSYCHIATRIC SYNDROMES ASSOCIATED WITH TBI

There have been few controlled clinical trials to assess the effects of medication in persons with TBI. As suggested above, the decision regarding which medication (if any) to prescribe is based on: 1) current knowledge of the efficacy of these medications in other psychiatric disorders, 2) side effect profiles of the medications, 3) the increased sensitivity to side effects shown by patients with brain injury, 4) analogies from the brain injury symptoms to the recognized psychiatric syndromes (i.e., amotivational syndrome after TBI may be analogous to the deficit syndrome in schizophrenia), and 5) hypotheses regarding how the neurochemical changes after TBI may inform the

**TABLE 52-1**  
*General Principles of Pharmacotherapy for Patients with Traumatic Brain Injuries*

Start low, go slow	Initiate treatment at doses lower than those used in patients without brain injuries, and raise doses more slowly than in patients without brain injuries.
Adequate therapeutic trial	Although patients with brain injuries may be more sensitive to the side effects of many medications, standard doses of such medication may be needed to treat adequately the neuropsychiatric problems of these patients.
Continuous Reassessment	The need for continued treatment should be reassessed in an ongoing fashion, and dose reduction or medication discontinuation should be attempted after achieving remission of target symptoms. Spontaneous recovery occurs, and in such circumstances continued pharmacotherapy is unnecessary.
Monitor drug-drug interactions	Because patients with brain injuries are often sensitive to medication side effects and because they may require treatment with several medications, it is essential to be aware of and to monitor these patients for possible drug-drug interactions.
Augmentation	A patient experiencing a partial response to treatment with a single agent may benefit from augmentation of that treatment with a second agent with a different mechanism of action. Augmentation of partial responses is preferable to switching to an agent with the same pharmacologic profile at that producing the partial response.
Symptom Intensification	If targeted psychiatric symptoms worsen soon after initiation of pharmacotherapy, lower the dose of the medication; if symptom intensification persists, discontinue the medication entirely.

selection of medications based on current understanding of their proposed mechanisms of action.

There are several general guidelines that should be followed in the pharmacological treatment of the psychiatric syndromes that occur after TBI (see Table 52-1). In summary, these principles are:

- 1 Start low and go slow with regard to dosing.
- 2 Undertake a therapeutic trial of medications – define the target symptom, outcome, and treatment period clearly before treatment and adhere to the proposed treatment plan as much as possible.
- 3 Continuous reassessment of clinical condition, again using standardized scales to anchor that assessment wherever possible.
- 4 Identify possible drug-drug interactions prior to treatment and assess any adverse effects of treatment with this possibility in mind.
- 5 Augment partial response – if a single agent confers only incomplete relief of symptoms, consider augmenting that treatment response with an agent of different pharmacologic mechanism before discontinuing altogether a medication that is partially effective.
- 6 Discontinue or lower the dose of the most recently prescribed medication if there is a worsening of the treated symptom soon after the medication had been initiated (or increased).

Experienced clinicians often report that persons with TBI of any type are more sensitive to the side effects of

medications than are patients with similar psychiatric problems but no brain injury. Although our own experience echoes this suggestion, it is important to acknowledge that studies demonstrating increased medication sensitivity following TBI are few and that many persons with TBI appear to tolerate these medications reasonably well even at standard therapeutic doses. Nonetheless, it is prudent to raise and lower doses of psychotropic medications in relatively small increments over relatively longer time periods than might be done in general psychiatric practice (i.e., to use a “start low, go slow” approach).

When psychotropic medications are prescribed, it is important that they are given in a manner that increases the probability of benefit and minimizes the possibility of adverse reactions. It is also important that such medications be given sufficient time to impart their full effects. Thus when a decision is made to administer a medication, the patient must be offered a robust therapeutic trial of that medication, including gradual titration to maximally tolerated doses and maintenance of treatment for a period of time sufficient to fully evaluate their potential therapeutic effects. While it is important to alleviate the suffering of patients as quickly as possible, many psychotropic medications (e.g., antidepressants, anti-aggressive agents, etc.) must often be used for many weeks or longer before their benefits become fully apparent.

As noted above, continuous reassessment of neuropsychiatric symptoms during treatment is necessary to determine whether each prescribed medication is still required, particularly early after a TBI. Spontaneous recovery in the early post-injury period may change both

the need for such treatments and also their effects (beneficial and adverse) at a given dose in a dynamic fashion. Use of the aforementioned structured assessments (Neurobehavioral Rating Scale, Neuropsychiatric Inventory) may be of use in this regard, as these multidimensional scales permit both ongoing assessment of both target symptom response and also a measure with which to monitor for the development of new neuropsychiatric symptoms.

Although the literature regarding the pharmacotherapy of neuropsychiatric disturbances is evolving rapidly, few studies offer information regarding the optimal duration of these treatments and/or the issues pertaining to treatment discontinuation and relapse risk. Because spontaneous remission of some symptoms occurs over time, a previously necessary medication may at some point thereafter become unnecessary. If the patient has responded favorably to initial medication treatment for one or another neuropsychiatric problem after TBI, the clinician must use sound judgment and work together with his or her patient (and/or caregiver) in order to decide whether and/or when to taper and attempt to discontinue that treatment. In some cases, carryover effect of the medication may occur (i.e., its effects may persist after the duration of treatment), in which case a reinstatement of the medication may not be required. Extrapolating from treatment guidelines established for analogous conditions in persons without brain injury may be of some use in such medical decision-making. For example, the standard guidelines for the treatment of major depression offered by the American Psychiatric Association (2000) (6), which suggest that antidepressant treatment should be continued for 16–20 weeks following remission of depressive symptoms, may offer a reasonable framework within which to develop a treatment plan for post-traumatic neuropsychiatric disturbances.

When a new medication is initiated in combination with medications previously prescribed, the clinician must be vigilant for the development of drug-drug interactions. These interactions may include alteration of pharmacokinetics that result in increased half-lives and serum levels of medications, such as those that occur with the use of anticonvulsants or other agents that markedly affect hepatic metabolism or renal elimination. Additionally, alterations of pharmacodynamics may develop during the administration of medications with additive or synergistic clinical effects, such as increased sedation when several medications with otherwise tolerable sedative effects are administered simultaneously.

If a patient does not respond favorably to the initial medication prescribed, several alternative treatments are usually available. If there has been no response to treatment, switching to a medication with a different mechanism of action is suggested, much as is done in the treatment of patients without brain injuries. If there has

been a partial response to the initial medication, addition of another medication with a different mechanism of action may be both useful and more beneficial than abandoning entirely treatment with the partially effective agent. The selection of a supplementary (or augmenting) medication should be based on consideration of the possible complementary or contrary mechanisms of action of such agents, the individual and combined side effect profiles of the initial and secondary agents, and their potential pharmacokinetic and pharmacodynamic interactions.

While persons with TBI may experience multiple concurrent neuropsychiatric symptoms (i.e., depressed mood, irritability, poor attention, fatigue, and sleep disturbances) that seem to suggest a single “psychiatric diagnosis” such as major depression, it is not uncommon to observe persistence of some of these symptoms despite treatment of the apparent diagnosis. In other words, diagnostic parsimony should be sought but may not always be the best or most accurate diagnostic approach in this population. The neuropsychiatric approach of evaluating and monitoring individual symptoms is often the most useful one, even though it diverges from the more typical “syndromal” approach to treatment that is common in conventional psychiatric practice. In short, several medications may be required to alleviate several distinct posttraumatic neuropsychiatric symptoms. Nonetheless, it is prudent to initiate each treatment sequentially rather than concurrently in order to understand as clearly as possible both the beneficial and adverse effects of each medication prescribed.

Studies of the effects of psychotropic medications in patients with TBI are few, and rigorous double-blind placebo-controlled studies are rare (7). The recommendations contained in this chapter represent a synthesis of the available treatment literature in TBI, extensions of the known uses of these medications in phenotypically similar psychiatric populations, patients with other types of brain injury (e.g., stroke, multiple sclerosis, etc.), and the opinions of the authors based on our review of this literature. While recognizing that the pathophysiology of neuropsychiatric symptoms may differ between patients with TBI and those whose neuropsychiatric symptoms arise in the context of other neurological conditions or psychiatric disorders, and while acknowledging that generalization of response to treatment seen in the context of other forms of brain dysfunction (e.g., stroke, Alzheimer’s disease, schizophrenia) to TBI may not always be valid, the intent of this chapter is to offer clinicians guidance regarding the pharmacotherapy of posttraumatic neuropsychiatric disturbances. Where such are not available at all, we offer recommendations based on our experience in this area. Although it is our hope that such recommendations will be of use to clinicians working with persons with TBI, it is important to note that anecdotally-based recommendations must be regarded as entirely preliminary.

## PHARMACOLOGICAL TREATMENT OF SPECIFIC NEUROPSYCHIATRIC SYNDROMES

Posttraumatic neuropsychiatric symptoms are amenable to treatment with a variety of medications. In the following section, we review briefly each of the major neuropsychiatric symptoms and syndromes that may develop after TBI and discuss their most common pharmacologic treatments. This section is organized according to symptom and/or syndrome, and within each section pharmacotherapies are organized by medication class. Where such are able to be offered based on the literature, recommendations regarding the use of these medications and cautionary notes regarding their side effects are presented.

### EMOTIONAL DISTURBANCES

Emotional disturbances, including mood disorders and disorders of affect regulation, are common consequences of TBI and may be very detrimental to a patient's rehabilitation and socialization (8–12). The literature regarding treatment of these conditions after TBI is limited when compared to that for phenotypically similar primary psychiatric disorders, but is actively developing.

#### Depression

Depression after TBI is amenable to pharmacologic intervention, and may alleviate not only the mood disturbance but also reduce other postconcussive symptoms and the patient's experience of the severity of such symptoms (13). Although many factors (i.e., sleep disturbance, fatigue (anergia), difficulty concentration, anhedonia (apathy), etc.) may produce or contribute to apparent depressive symptoms, when there are sufficient symptoms to merit a diagnosis of depression – regardless of their other possible causes – antidepressant treatment should be initiated. It is, however, particularly important to distinguish between depression (a state of excessive and persistent sadness) and apathy (in which there is a loss of emotional responsiveness) before initiating treatment for depression; there is minimal overlap between the treatment of these conditions, and mistaking one of these conditions for the other may delay the delivery of the most appropriate treatments.

Somatic therapies for depression following TBI include several classes of antidepressant medications, including selective serotonin reuptake inhibitors, tricyclic and tetracyclic agents, novel antidepressants, monoamine oxidase inhibitors, and electroconvulsive therapy.

#### *Selective Serotonin Reuptake Inhibitors*

The selective serotonin reuptake inhibitors (SSRIs) include fluoxetine, sertraline, paroxetine, citalopram, escitalopram,

and fluvoxamine. Given the relatively favorable profile of the selective serotonin reuptake inhibitors (SSRIs) when compared to other presently available classes of antidepressants, these agents are suggested as the first-line treatment for depression following TBI.

Among these, the best evidence at the present time favors sertraline as a first-line treatment for depression following TBI. Fann et al. (2000) (13) describe improvement in depression secondary to mild TBI using sertraline (dose range 25–200 mg by end of study) in an 8-week, nonrandomized, single-blind, placebo run-in trial. This study included 15 patients with major depression diagnosed 3–24 months following mild traumatic brain injury. Thirteen (87%) had a decrease in Hamilton Rating Scale for Depression score of (50% (“response”), and 10 (67%) achieved a score of (7 (“remission”) by treatment week 8. Significant improvements were also observed in ratings of psychological distress, anger and aggression, functioning, and postconcussive symptoms during treatment, and only one patient discontinued treatment due to side effects. Similarly, Turner-Stokes et al. (2002) (14) performed an open-label trial of sertraline for depression following brain injuries, including TBI, in 21 adult patients. They report clinical improvement as assessed by DSM-IV criteria in all of these patients. Among the 17 patients able to complete the Beck Depression Inventory before and after treatment, significant decreases in depressive symptoms were associated with treatment in this group. Of these, 11 had failed previous treatment with a different selective serotonin reuptake inhibitor. These findings echo those of Fann et al. (2000) (13) and suggest that sertraline may be of significant benefit for depression following brain injury.

In a subsequent report, Fann et al. (2001) (15) describe sertraline treatment-related improvements in psychomotor speed, recent verbal memory, recent visual memory, and general cognitive efficiency, as well as improvements in patient perception of cognitive symptoms. Schmitt et al. (2001) (16) investigated the cognitive effects of several SSRIs on posttraumatic cognitive impairments, and their observations support and possibly inform the observation of Fann et al. (2001) (15). Schmitt et al. (2001) (16) observed significant improvements in verbal fluency among healthy middle-aged adults treated with sertraline 50–100 mg when compared to treatment with placebo. They attributed the cognitive benefits of this treatment to sertraline's modest ability to inhibit dopamine reuptake. As discussed in the chapter on the pharmacotherapy of cognitive impairment elsewhere in this volume, such increases of dopamine would be expected to improve frontally-mediated cognitive and behavioral function in this population. However, Meythaler et al. (2001) (17) performed a placebo-controlled trial of sertraline for arousal and attentional impairments in 11 subjects with severe TBI in the acute rehabilitation setting



and failed to find a statistically significant treatment effect on these cognitive functions. Although the authors of this study caution against over-interpretation of this finding in light of their small sample size, their findings suggest that neither the serotonergic or dopaminergic reuptake inhibition properties of this agent are sufficient to produce marked improvements in cognition among persons with recent, severe TBI. It is possible that in the context of milder injuries, such as were experienced by subjects included in the Fann et al. (2001) study (13, 15), treatment with sertraline may confer cognitive benefits on the basis of resolving depression alone, as a result of sertraline's modest dopaminergic augmentation of frontal lobe function, or both. Additional studies are needed to clarify the effect of sertraline on cognitive function in persons with TBI and depression.

Sertraline may also be of benefit for the treatment of irritability and aggression following TBI even when it is without specific benefit on related depressive symptoms. Kant et al. (1998) (18) describe reductions in posttraumatic irritability and aggression (as assessed using the Overt Aggression Scale-Modified for outpatients) during treatment of 13 patients with sertraline at doses of 50 mg or greater. Although some changes in depressive symptoms (as assessed using the Beck Depression Inventory) were also observed, these were not of a degree sufficient to produce statistical significance. It is possible that the relatively low-doses of sertraline used in this study were inadequate for the treatment of depression, but were sufficient to treat irritability-predominant affective lability; this suggestion is consistent with other reports describing the effects of low-dose SSRIs on such symptoms (reviewed later in this chapter).

Collectively, these reports suggest that sertraline may be of benefit in the treatment of depression following TBI, and that such treatment may reduce other affective and postconcussive symptoms as well. As with all of the SSRIs, gastrointestinal side effects during treatment with sertraline are not uncommon, although these are in many patients dose-related and/or transient (i.e., associated with treatment initiation or dose escalation). The relatively short half-life (approximately 26 hours) of this agent permits development of steady-state plasma levels within the first week of treatment in most patients; consequently, relief from intolerable side effects, when such develop, is usually afforded shortly after treatment discontinuation.

Several reports suggest that fluoxetine may be of benefit in the treatment of depression following TBI, but may be associated with a higher rate of adverse effects than is treatment with sertraline. Cassidy (1989) (19) conducted an open-label trial using fluoxetine for 8 patients with severe TBI and associated depression. They observed marked improvement in two patients and moderate improvement in three patients. Half of these patients experienced sedative side effects, and 3 out of 8 patients

reported an increase in anxiety. Wroblewski et al. (1992) (20) report a case in which fluoxetine 20 mg/day reduced depressive symptoms after treatment with desipramine alleviated depressive symptoms but precipitated post-traumatic seizures. At least one other report suggests that fluoxetine may be both useful and well-tolerated: Bessette and Peterson (1992) (21) observed a favorable response to fluoxetine 20 mg/day in a 41-year-old woman who experienced an episode of major depression after a minor brain injury.

Horsfield et al. (2002) (22) performed an eight-month open-label study of the effects of fluoxetine 20–60 mg/day in five patients with TBI and varying levels of depression in order to determine whether this medication conferred mood and/or cognitive benefits. They observed improvements in mood as well as improvement on several measures of attention, processing speed, and working memory in this small group of patients. Their findings are consistent with the observations of Fann et al. (2001) (15) with respect to an association between improvements in posttraumatic depressive and cognitive symptoms. Horsfield et al. (2002) (22) suggest that fluoxetine's ability to stimulate expression of brain derived neurotrophic factor and its specific tyrosine kinase receptor, which has in rodents been demonstrated to produce neuritic elongation and increased dendritic branching density of some hippocampal neurons, may explain the apparent benefits of this agent on posttraumatic cognitive impairments. While their suggestion is intriguing, support for it in experimental injury models is lacking. For the present, it is simpler to interpret their findings as reflecting the well-known activating effects of fluoxetine.

As with sertraline, the most common side effects of fluoxetine are gastrointestinal and these are often dose-related and/or transient. It is of note that anxiety and insomnia occur in approximately 20% of patients without brain injuries (23), which may offer some explanation for the rate of treatment-emergent anxiety associated with fluoxetine (19). Additionally, seizure during treatment with fluoxetine in a brain-injured patient has been reported (20). However, it is difficult to draw any conclusions regarding the safety (or efficacy) of this medication with respect to either seizure or any other adverse effects based upon the available literature. The authors remain circumspect with regard to the potential for fluoxetine to lower significantly the seizure threshold among persons with TBI, including those with post-traumatic epilepsy, based on our success with the use of this medication among persons with TBI. Nonetheless, the published observation of precipitation of post-traumatic seizures with this and other antidepressant medications (see below) suggests that the possibility of altering seizure threshold by their administration should not be dismissed offhandedly. At a minimum, we suggest that this possibility be discussed during the process of providing patients

with informed consent to treatment with these (or almost any) antidepressant agents.

Two case reports describe problematic drug-drug interactions with fluoxetine in persons with TBI. The first describes new-onset dysarthria and “speech blocking” when fluoxetine was added to trazodone in a man with a fall-related TBI (24). Both of these treatment-emergent symptoms resolved following discontinuation of fluoxetine. The second report describes the development of hypomania in a woman with depression following TBI who added St John’s wort and Ginkgo biloba to her ongoing regimen of fluoxetine and buspirone (25). Her hypomania remitted following discontinuation of these herbal agents. While these cases are presented in the context of fluoxetine for depression following TBI, it is important to note that these and other drug-drug interactions are possible during treatment with any of the SSRIs. As such, the reporting of such cases may or may not reflect a propensity for problematic drug-drug interactions with fluoxetine *per se*.

Despite these reports, we do not regard the rate of adverse effects during treatment with fluoxetine to be so problematic that its use in this population is precluded. In clinical practice, patients often benefit from treatment with this agent, and do so without untoward effects in the majority of cases. However, it is important to note that the average half-life of the primary and active metabolite of fluoxetine, norfluoxetine, is on average at least six days. Given that elimination of this metabolite requires 4–5 half-lives to complete, patients who develop treatment-emergent adverse effects with fluoxetine may continue to experience such effects for several weeks following treatment discontinuation. Therefore, while fluoxetine appears to be a reasonably effective treatment for depression following TBI, the possibility of prolongation of adverse effects during treatment of this agent makes it somewhat less favorable for this purpose than sertraline.

Paroxetine may be a useful treatment for depression in some patients, although there is at present only a single case report describing its use for the treatment of depression following TBI in a patient with “personality change – labile type due to traumatic brain injury” (26). The patient described might be understood as experiencing affective lability with some depressive features, and as such it is not clear that this study can be used to support the use of this medication for fully symptomatic depression following TBI. Nonetheless, paroxetine is in some cases used for this purpose and may be of benefit.

As with the other SSRIs, the most common side effects produced by paroxetine are gastrointestinal. Sedation is also a common side effect of paroxetine, occurring in almost 25% of general psychiatric patients receiving it (23). Additionally, this agent possesses more significant antimuscarinic properties than the other SSRIs (16, 27). These properties contribute to systemic anticholinergic

side effects such as dry mouth and constipation, and also pose risk for exacerbating cognitive impairments among persons with TBI. For example, Schmitt et al. (2001) (16) demonstrated that healthy middle-aged adults experienced significantly greater impairments of delayed recall in a word learning test during treatment with paroxetine 20–40 mg/day than during treatment with placebo, an effect that was attributed to paroxetine’s antimuscarinic properties. Given that TBI is associated with reduced cholinergic function in a significant number of patients (see Chapter 53), one would predict that this might place persons with TBI at risk for similar or greater degrees of cognitive impairment during treatment with this agent. Although this remains speculation at present, clinicians should remain mindful of this possibility when undertaking treatment with paroxetine in this population. As with fluoxetine, both the available literature and the potential for adverse cognitive effects of this agent suggest that paroxetine should be considered as a less favorable agent than sertraline for the treatment of depression following TBI.

At the time of this writing, the only report describing treatment with citalopram does so in combination with carbamazepine for the treatment of mood and other neurobehavioral problems following TBI (28). In an open-label fashion, subjects in this study were treated with 12 weeks of citalopram 20 mg/day and carbamazepine 600 mg/day. Clinical Global Impression ratings and Brief Psychiatric Rating Scale scores were determined before and after treatment with these agents, and were significantly improved by this combination therapy. These authors note that subjects with more remote TBI (24–36 months prior to study) improved to a lesser degree than did subjects with more recent TBI (within 6 months). It is not clear whether this observation reflects spontaneous recovery among the more recently injured subjects during the treatment period (i.e., a false-positive treatment response) or instead suggests improved treatment responsiveness in the early period following TBI. Additionally, the concurrent administration of both agents precludes attribution of the symptomatic improvements observed by the authors to either one of these agents alone.

As with the other SSRIs, common clinical experience suggests that some patients with depression following TBI will benefit from treatment with citalopram. The side effect profile, limited propensity for drug-drug interactions, and relatively short half-life of this agent make it attractive for use among persons with TBI. However, its use should be undertaken with caution pending additional data regarding its effectiveness and tolerability in this population.

At present, there are no reports regarding the use of either escitalopram or fluvoxamine for the treatment of depression following TBI. Our experience suggests that escitalopram is the more effective of these two for this

purpose and is similar to citalopram with respect to efficacy, tolerability, and drug-drug interactions. However, these agents should be used with caution pending further study of their effects and side effects among persons with depression following TBI.

### *Tricyclic and Tetracyclic Agents*

The development and use of tricyclic and tetracyclic antidepressants (TCAs) for posttraumatic depression antedates that of the SSRIs. The TCAs include imipramine, amitriptyline, trimipramine, desipramine, nortriptyline, maprotiline, doxepin, and protriptyline. Since the advent of the SSRIs, the TCAs are used less commonly as first-line agents for the treatment of depression in general as well as for depression following TBI. This may in part reflect concerns regarding the possibility of increased side effects associated with these agents, reports of more limited effectiveness of these agents among persons with TBI, waning familiarity with the use of these agents on the part of recently trained clinicians, or some combination of these factors. Regardless of the reasons for the more limited use of TCAs presently, there is less evidence to support the use of these agents for the treatment of depression following TBI than for the SSRIs. Additionally, there is evidence suggesting that these agents may not be as effective in the treatment of depression following TBI as they are for idiopathic major depressive episodes.

For example, Saran (1985) (29) conducted a crossover study of phenelzine and amitriptyline administered at therapeutic doses to ten patients with "minor brain injury" and twelve patients with major depressive symptoms but without TBI. All of the patients with idiopathic major depressive symptoms improved after 4 weeks of amitriptyline but none of the TBI patients improved. More recently, Dinan and Mobayed (1992) (30) reported 85% of patients with major depressive disorder responded to amitriptyline while only 31% of similarly depressed TBI patients responded to this treatment. In contrast to these discouraging reports, Varney et al. (1987) (31) found that 82% of 51 patients with major depressive disorder and TBI who received treatment with either TCAs or carbamazepine reported at least moderate relief of depressive symptoms. Collectively, these observations offer only modest support, at best, for the use of amitriptyline for depression following TBI. The authors do not recommend use of amitriptyline as a first-line therapy for the treatment of posttraumatic depression both as a result of its modest beneficial effects in this population and in light of the availability of newer, less problematic, and more consistently effective antidepressants.

Among the newer TCAs, nortriptyline and desipramine are used more commonly in clinical practice. However, there remains very limited evidence to guide their use and with which to assess the risks entailed by their use

in persons with TBI. Wroblewski et al. (1996) (32) performed a modified, blinded, placebo lead-in treatment study of ten patients with depression following severe TBI using desipramine and observed improvement in six of seven (86%) of patients able to complete the study. However, three patients (30%) discontinued the study, including one that developed seizures and one that developed treatment-emergent mania. An additional patient experienced a seizure during treatment with desipramine but continued treatment with this medication nonetheless. While this study suggests that desipramine may be effective for the treatment of depression in some persons with TBI, its use may also be associated with more significant adverse effects than the SSRIs. A single report offers little evidence with which to guide clinical practice, but the findings from this study should be considered by clinicians and their patients prior to undertaking treatment with desipramine as a first-line agent.

When a TCA is prescribed for depression following TBI, nortriptyline is the one used most often. This may in part reflect its more favorable side effect profile in comparison to the other TCAs as well as its established effectiveness for the treatment of depression following stroke (33). However, stroke is not pathophysiologically equivalent to TBI, and studies describing antidepressant efficacy following stroke may not be equally applicable to the treatment of depression following TBI. Both stroke and TBI may produce discrete white matter lesions that interrupt catecholaminergic or serotonergic pathways, and mood disorders following such injuries may result from dysfunction in these neurotransmitter systems. However, many persons with TBI do not suffer discrete lesions to these systems, but instead experience diffuse axonal injuries. The latter may modestly affect ascending catecholaminergic or serotonergic pathways, but also disrupts glutamatergically-dependent systems, cholinergic projections, other cortico-cortico and cortico-subcortical pathways, and cortical and subcortical structures. Additionally, TBI commonly involves bihemispheric injury, whereas as bihemispheric injury is rare following a single stroke. Therefore, the neuroanatomic and neurochemical consequences of TBI may not be equivalent to those resulting from stroke. These differences would suggest that there should be differences in both antidepressant treatment effects and also side effects in these two populations.

Based on the available evidence, we regard SSRIs as first-line treatment for depression following TBI. In the event that these agents fail and a TCA is considered subsequently, we suggest use of either nortriptyline (initial doses of 25 mg/day) or desipramine (initial doses of 25 mg tid) following careful informed consent of the patient regarding the potential side effects and complications of these treatments. Treatment should proceed slowly, with incremental dose increases no more often than weekly.

Careful monitoring of plasma levels of the parent compound and its major metabolites should be undertaken, with a goal of driving levels into the therapeutic range while assessing the clinical effects of treatment at such doses/levels (e.g., nortriptyline levels 50–100  $\mu\text{g/mL}$ ; desipramine levels greater than 125  $\mu\text{g/mL}$ ).

The most common and disabling side effects of tricyclic and tetracyclic antidepressants in patients with neurological disorders are those associated with the anticholinergic properties of these medications, which can impair attention, concentration, and memory. For example, patients with Parkinson's disease not infrequently experience increased confusion when treated with anticholinergic medications (34, 35). Experimental evidence in traumatically brain-injured rats supports this observation (36, 37), as does common clinical experience in the treatment of patients with TBI. Such observations are consistent with the observed effects of both experimental and human TBI on cortical cholinergic function. Amitriptyline, trimipramine, doxepin, protriptyline have high affinities for the muscarinic receptors. Given their strong anticholinergic properties, these medications should be prescribed only after careful consideration (and preferably empiric trials) of potentially less problematic antidepressants.

If side effects such as sedation, confusion, or symptomatic hypotension (orthostatic or otherwise) develop, dose reductions may either alleviate these effects and/or permit patients time to accommodate to them. If the patient's side effects abate following such dose reduction, gradual dose escalation may in some cases proceed without recurrence of these side effects. However, when these or other side effects limit TCA dosing to sub-therapeutic levels, either augmentation strategies or a switch to a different medication may need to be considered.

TCAs also may be associated with non-trivial rates of serious adverse events, and in particular seizures. Wroblewski et al. (1990) (38) reviewed the records of 68 patients with TBI who received antidepressant, and predominantly tricyclic antidepressant, treatment for at least 3 months. The frequency of seizures was compared for the 3 months before treatment, during treatment, and after treatment. Seizures occurred among 6 patients during the baseline period, 16 patients during antidepressant treatment, and 4 patients after treatment was discontinued. Fourteen patients (20%) had seizures shortly after the initiation of treatment. For 12 of these patients, no seizures occurred after treatment with the antidepressant was discontinued. Importantly, 7 of these patients were receiving anticonvulsant medication before and during antidepressant treatment. Also, the occurrence of seizures was related to greater severity of brain injury. Although our experience suggests that the rate of seizures during treatment with TCAs in the late period following TBI is not as high as that observed by Wroblewski et al. (1990) (38),

clinicians should be mindful of the potential for this serious adverse effect when prescribing TCAs to persons with TBI.

### *Novel Antidepressants Duloxetine*

The novel antidepressants include venlafaxine, mirtazapine, trazodone, nefazodone, and bupropion. Khouzam and Donnelly (1998) (39) report a reduction in TBI-induced compulsive behavior in response to treatment with venlafaxine. Teng et al. (2001) (40) describe the use of bupropion for treatment-resistant restlessness in a patient with severe TBI during acute rehabilitation. However, at the time of this writing neither these nor any other reports offer describe the beneficial or adverse effects associated with the use of these agents for the treatment of depression following TBI.

Common clinical experience suggests that many of these agents may be useful in the treatment of depression following TBI, but their use must be undertaken knowing that there has been no published information in this population to assist clinicians in ascertaining likelihood of benefit and the risk of adverse consequences. Due to the concern about hepatotoxicity with nefazodone, we reserve this medication for individuals who have not been responsive or tolerant to other antidepressants. Of note, bupropion is often suggested to be associated with a higher incidence of seizures in otherwise healthy psychiatric patients (41, 42). Such suggestions prompt caution prior to prescribing these agents in patients with depression following TBI. However, Johnston et al. (1991) (43), in a 102-site study of 1, 986 patients treated with bupropion for depression, report seizure rates of 0.24–0.40%. Among patients receiving bupropion 300 to 450 mg/day, the cumulative rate of seizure was 0.36%. This large data set suggests that bupropion may not be more likely to reduce seizure threshold than other antidepressants. Whether the same is true of bupropion's effects on seizure threshold following TBI is not at present clear. While it may be overly cautious to suggest avoiding use of this agent for the treatment of depression following TBI, in the absence of additional data clinicians should regard bupropion as likely to demonstrate the same dose-dependent seizure risk in persons with TBI as in the general population, and should consider the possibility that the dose at which this increased risk emerges may be lower among persons with TBI than in the general population. Pending clarification of this issue, bupropion should be considered a second-line treatment for depression following TBI.

### *Monoamine Oxidase Inhibitors*

Monoamine oxidase inhibitors (MAOIs) are not often used in persons with depression following TBI. This may reflect the high likelihood of difficulties with patient

adherence to the complex dietary restrictions required during use of these medications, and particularly among persons with significant posttraumatic cognitive impairments. Additionally, the literature offers little support for the effectiveness of these medications in the TBI population. In the studies by Saran (1985) (29) and Dinan and Mobayed (1992) (30) described above, phenelzine was not beneficial for the treatment of posttraumatic depression, including depression that had failed to respond to treatment with amitriptyline. Moclobemide, a selective, reversible MAO-A inhibitor, afforded improvement in 23 of 26 (88%) of patients with depression following TBI (44). Because moclobemide reversibly inhibits the isoenzyme MAO-A, its use does not entail the strict dietary prohibitions associated with other MAOIs. However, moclobemide is not available in the United States.

### *Other Agents*

Depressed mood due to TBI may respond to treatment with methylphenidate. Gualtieri and Evans (1988) (45) reported significant improvement on ratings of mood and cognitive performance among 15 patients with TBI following treatment with methylphenidate using a double blind, placebo-controlled crossover design study. These results were modest but suggestive of a possible role for methylphenidate in the treatment of both cognitive and mood disturbances following TBI. Although other studies offer support for the role of methylphenidate in the treatment of cognitive impairment following TBI (see Chapter 53), it is not clear if or for how long such benefits on either mood or cognition might be sustained by this treatment. Common clinical experience suggests that dextroamphetamine may be similar in its effects on mood and cognition following TBI, but no reports document a clear role for this medication in the treatment of depression following TBI.

We suggest that these medications be regarded as potential adjunctive rather than primary agents for the treatment of depression following TBI, particularly among patients with both significant depressive symptoms and also marked cognitive impairments of the sort that usually respond to treatment with stimulants (see Chapter 53).

### *Electroconvulsive Therapy*

Electroconvulsive therapy (ECT) remains a highly effective and underutilized modality for the treatment of depression in general, and it appears to be an effective treatment of depression following acute TBI (46–48). Kant et al. (1999) (49) reported on the safety and efficacy of ECT in patients with head injury in a retrospective review of 11 patients hospitalized as a result of neuropsychiatric problems after TBI. Of these subjects,

9 experienced a major depression or other mood disorder due to TBI. All of these patients responded favorably to ECT as assessed by the Montgomery-Asberg Depression Rating Scale and Global Assessment of Functioning Scale, and did so without significant adverse cognitive or physical sequelae. Functional improvement occurred irrespective of baseline cognitive functioning or severity of injury. These studies suggest that ECT may be a safe treatment for chronic and severe neuropsychiatric disorders due to TBI. When used, we recommend treatment with the lowest possible energy levels that will generate a seizure of adequate duration (greater than 20 seconds), using pulsatile currents, increased spacing of treatments (2–5 days between treatments), and fewer treatments in an entire course (four to six). If the patient also suffers from significant cognitive (especially memory) impairments due to TBI, nondominant unilateral ECT may be the preferred technique if this treatment is used.

### *Seizures and Antidepressants*

As noted above, some SSRIs, TCAs, and novel antidepressants may increase the risk for seizures during treatment of depression following TBI. This issue is raised frequently in clinical practice, but the magnitude of the risk posed by such treatments is unclear. Among patients with established epilepsy, Ojemann et al. (1987) (50) found that seizure control does not appear to worsen if psychotropic medication is introduced cautiously and if the patient is on an effective anticonvulsant regimen. There are, at present, no indications that treatment of depression in patients with posttraumatic epilepsy differs from that in patients with epilepsy of other etiologies. While we conclude that antidepressants can be used safely and effectively in patients with TBI, including patients with post-traumatic epilepsy, we recommend that these agents be prescribed with caution and that treatment with them include assiduous monitoring for change in seizure frequency.

### *Other Drug-Drug Interactions with Antidepressants*

In addition to those already noted above, there are several important drug interactions that may occur among antidepressants and other drugs commonly prescribed for neurological conditions (51). Many antiparkinsonian drugs and neuroleptics have anticholinergic effects that are additive to those of the antidepressants. Antidepressant levels are likely to be decreased—often below therapeutic range—by the anticonvulsants phenytoin, carbamazepine, and phenobarbital. Similarly, antidepressants such as fluoxetine may raise the plasma levels of the anticonvulsants phenytoin (52), valproic acid (53), and carbamazepine (54). Carbamazepine induces the metabolism of sertraline, and may therefore entail increased doses of the latter

during treatment with the former. Patients receiving treatment with medications that require therapeutic blood level monitoring should have more frequent monitoring when antidepressants are administered.

### **Mania**

Mania and bipolar disorder are less common consequences of TBI, although we believe that they are often underdiagnosed conditions in this populations. Treatment of acute manic states may include any of several pharmacologic approaches, including use of atypical antipsychotics, typical antipsychotics, anticonvulsants, and/or benzodiazepines. Prophylaxis against manic episodes is typically undertaken with lithium carbonate, carbamazepine, or valproate. There are very few reports regarding the treatment of mania following TBI (discussed below), whether that treatment is for acute manic states or for long-term prophylaxis against recurrent mania. The studies performed to-date suggest that treatment with lithium carbonate, carbamazepine, and valproate may be useful in this population as well.

Although there is emerging enthusiasm in general psychiatry for the use of other agents, including several of the newer anticonvulsants (e.g., lamotrigine, oxcarbazepine) and atypical antipsychotics (e.g., risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, etc.) for prophylactic treatment of persons with bipolar disorder, there are no reports regarding the use of these agents in persons with TBI. In light of the uncertainty regarding the efficacy and safety of these agents in this population, these agents will not be considered here in detail for this purpose. Clinicians interested in applying these agents to the treatment of persons with mania due to TBI are advised to undertake such treatments as a second-line effort following trials of the agents for which there is published data and/or after consultation with an expert in the treatment of secondary manic syndromes.

### **Lithium**

Several small cases series suggest that lithium carbonate may be useful for the treatment of mania following TBI, although partial response, relapse of symptoms, or need for a second mood stabilizer are common (55–60). Lithium appears more likely to produce nausea, tremor, ataxia, and lethargy in persons with neurological disorders than in the general psychiatric population. In addition, lithium may lower seizure threshold (61). Additionally, patients with mania after TBI may respond to treatment with lithium despite relatively low blood levels (e.g., 0.2–0.5 mEq/L). Collectively, these observations highlight the need for both a “start-low, go-slow” approach to the care of these patients and also a dosing strategy that targets symptoms rather than ostensibly “therapeutic” blood levels.

As a cautionary note, lithium has been reported to aggravate confusion in patients with brain damage (62). Consistent with that report, Hornstein and Seliger (1989) (63) reported a patient with preexisting bipolar disorder who experienced a recurrence of mania after closed head injury. This patient’s mania, before injury, was controlled with lithium carbonate without side effects. However, subsequent to brain injury, impaired attention emerged during treatment and abated when the lithium dose was lowered. Because lithium carbonate may exacerbate cognitive impairments or cause confusion, especially in combination antidepressants, anticonvulsants, and antipsychotic medications, we suggest limiting the use of lithium in patients with TBI to those with mania or recurrent depressive illness that preceded their brain damage and who previously responded well to this treatment. To minimize lithium-related side effects, we begin with low doses (300 mg/day) and titrate cautiously to beneficial effect or medication intolerance.

### **Carbamazepine**

Manic episodes occurring after TBI may also respond to carbamazepine (64, 65), although sometimes only after addition of lithium (65) or antipsychotics (57, 66). Because carbamazepine may produce or exacerbate cognitive impairments among persons with TBI (67), monitoring for this adverse effect when using this agent in patients with TBI is suggested. Additionally, brain injury appears to increase susceptibility to neurotoxicity induced by combination therapy with carbamazepine and lithium (55). For patients with mania subsequent to TBI, carbamazepine should be initiated at a dosage of 200 mg BID and in most cases adjusted to obtain plasma levels of 8–12 µg/ml. As with lithium, targeting symptoms is more important than adjusting dosing to achieve a specific blood level.

As is true for patients without histories of TBI, clinicians should be aware of the potential risks associated with carbamazepine treatment, particularly bone marrow suppression (including aplastic anemia) and hepatotoxicity. Complete blood counts and liver function tests should be regularly monitored (68). The most common signs of carbamazepine-induced neurotoxicity include lethargy, confusion, drowsiness, weakness, ataxia, nystagmus, and increased seizures. Pleak et al. (1988) (69) described the development of mania, irritability, and aggression with carbamazepine treatment. In our experience, this reaction is highly unusual and does not reflect a problem of serious concern regarding the use of carbamazepine for posttraumatic mania more generally.

### **Valproate**

Pope et al. (1988) (70) suggest that sodium valproate may be a useful mood stabilizer for patients with symptoms of

bipolar disorder following TBI, and Monji et al. (1999) (71) suggest that this benefit may extend to patients with rapid cycling mood disorders following TBI. In these retrospective report, patients with such symptoms after TBI appeared to respond more robustly than those with similar symptoms in the absence of TBI (88% vs 46%). The small sample sizes in this study do not permit extrapolation of this observation to TBI patients more generally, but are nonetheless encouraging of the use of this medication in the TBI population.

At present, we regard valproate as first-line treatment for mania following TBI. Valproate is begun at a dosage of 250 mg BID and gradually increased to obtain plasma levels of 50–100 µg/ml. As with carbamazepine, valproate may exacerbate cognitive impairments (67), although it appears less likely to do so than either carbamazepine or lithium. Nonetheless, its use should include careful and ongoing assessment of cognition. Tremor, weight gain, and diarrhea are common side effects of valproate. Although most patients tolerate valproate-induced tremor reasonably well, treatment-related weight gain is a common reason for treatment discontinuation. Hepatotoxicity is rare complication of treatment with valproate, and its occurrence is more commonly observed among children receiving concurrent treatment with multiple anticonvulsants (72).

#### *Other Anti-Manic Agents*

For mania or manic-like syndromes after TBI that do not respond to conventional mood-stabilizing therapies, relatively more novel approaches may be useful to consider. As noted earlier in this section, newer anticonvulsant agents and/or atypical antipsychotics are sometimes used in clinical practice with reasonable effect. There are no data at present with which to guide selection or inform treatment expectations, so clinicians should proceed with caution and vigilance for treatment-emergent side effects when using these agents.

Bakchine et al. (1989) (73) describe a manic-like state in a 44-year-old right-handed woman with bilateral orbitofrontal and right temporoparietal traumatic contusions that responded to clonidine after the patient's behavior failed to respond to carbamazepine and worsened with levodopa. Dubovsky et al. (1987) (74) and Levy and Janicak (2000) (75) suggest that verapamil may be a useful agent for the treatment of mania, whether this agent is used alone or in combination with other mood stabilizers. To-date, there are no studies of verapamil for the treatment of mania following TBI, but this agent might be worth considering when other conventional treatments fail or produce intolerable side effects. Clark and Davison (1987) (76) also report that ECT effected improvement in manic symptoms following non-penetrating trauma, and the authors suggest that this therapy may be valuable

to consider among persons with posttraumatic mania that fail to respond to pharmacotherapy for this condition.

#### **Affective Dysregulation (affective lability and pathologic crying/laughing)**

In contrast to mood disorders, conditions in which the baseline emotional state is pervasively disturbed over a relatively long period of time (i.e., weeks), disorders of affect denote conditions in which the more moment-to-moment variation and regulation of emotion is disturbed. The classic disorder of affective dysregulation is pathological laughing and/or crying (PLC), also known as “emotional incontinence” or “pseudobulbar affect.” Patients with this condition experience episodes of involuntary crying and/or laughing that may occur many times per day, are provoked by trivial (i.e., not sentimental) stimuli, are quite stereotyped in their presentation, uncontrollable, do not evoke a concordant subjective affective experience, and do not produce a persistent change in the prevailing mood (77). In this classic presentation, PLC appears to be a relatively infrequent (5.3%) consequence of TBI (78). Affective lability differs from PLC in that both affective expression and experience are episodically dysregulated, the inciting stimulus may be relatively minor but is often somewhat sentimental, the episodes are somewhat more amenable to voluntary control, and the paroxysms of affect are less stereotyped. As with PLC, these episodes do not produce a persistent change in mood. The prevalence of affective lability following TBI is not clear, although Jorge and Robinson (2003) (79) suggest a 1-year prevalence of approximately 12% among persons with TBI. Both PLC and affective lability are sources of significant distress and embarrassment to patients that otherwise, and quite correctly, report their mood as “fine” (euthymic). These conditions may not be understood properly by clinicians that interpret emotional disturbances only in terms of the DSM-based diagnostic system.

Although the neurobiology of mood and affect regulation overlap, the treatment of affective dysregulation in patients with brain injury overlaps with but is not identical to the treatment “uncomplicated” depression following TBI (80–84). The treatment literature overwhelmingly supports the use and effectiveness of relatively low-doses (often below typical antidepressant doses) of serotonergically and noradrenergically active antidepressants (82, 85–87), and to a lesser extent dopaminergic (88) and noradrenergic (89, 90), agents for the treatment of PLC and affective lability. Whether the lack of distinct therapies for these two disorders of affect reflects inseparable commonalities in their neurobiology or is instead an artifact of the diagnostic heterogeneity of patients included in the available treatment reports is unclear (11). It is noteworthy that the majority of treatment studies of these

problems derive from the stroke literature. Nonetheless, similar findings in multiple case series that include both persons with stroke and persons with TBI support the benefit of agents with serotonergic, dopaminergic, and noradrenergic properties for the treatment of PLC and/or affective lability following TBI.

### *Selective Serotonin Reuptake Inhibitors*

There are multiple reports of the beneficial effects of fluoxetine for “emotional incontinence” secondary to neurological disorders (81, 83) including TBI (84, 91). Brown and colleagues (1998) (92) treated 20 patients with post-stroke “emotionalism” (either PLC or affective lability) with fluoxetine in a double-blind placebo-controlled study. Those individuals receiving fluoxetine exhibited statistically and clinically significant improvement. In general, these investigators began treatment with 20 mg/day of fluoxetine, and patients often exhibited response within 5 days. The authors of this chapter have had similar success with fluoxetine both at low and also higher doses (40–80 mg/day) as well as with sertraline at doses ranging from 25–100 mg/day. A single-case report (93) and a small open label trial (94) demonstrated reductions in affective lability during treatment with paroxetine. The latter of these studies (94) also compared the effectiveness of paroxetine with citalopram for the treatment of affective lability after brain injury; while both medications effective for the treatment of affective lability, citalopram was the better tolerated medication. While only 2 of 26 patients included in the series described in this study were patients with TBI (the remainder being patients with strokes), both of these patients remained treated successfully for 1 year with paroxetine and experienced recurrent symptoms of affective lability after drug discontinuation. Andersen et al. (1999) (95) also describe improvement in episodic crying following TBI in a 6-year old child with citalopram 2.5 mg daily. As is often seen in the treatment of affective lability, treatment response occurred within 2 days of beginning treatment, a response more rapid than that usually encountered in the treatment of depressed mood/major depressive episode. Collectively, these reports suggest that the SSRIs are effective treatments for affective lability and PLC following TBI, and we recommend them as first-line agents for this purpose.

### *Tricyclic and Tetracyclic Antidepressants*

TCAs may also be effective for affective lability and PLC. Allman (1992) (96) described a marked decrease in pathological laughter in a patient treated with imipramine 150 mg/day, with improvement occurring by the second week of treatment. Common clinical practice, derived from the use of tricyclic antidepressant for PLC and affective lability following stroke (86), suggests that nortriptyline may

be of considerable benefit to patients with these conditions following TBI and may be effective at doses lower than those generally used to treat major depressive episodes (25–75 mg/day in many cases). However, we emphasize that for many patients it may be necessary to administer TCAs at standard antidepressant dosages to obtain full therapeutic effects, even when patients begin responding within days of initiating treatment at relatively low doses. Given the less favorable side effect profile of TCAs in this population, we recommend these as second-line agents for the treatment of affective lability and PLC following TBI.

### *Catecholaminergically-Active Agents*

Although psychostimulants and other medications that enhance dopamine and/or norepinephrine neurotransmission are used most often for the treatment of cognitive impairments and/or diminished motivation following TBI, they may also offer some relief from affective lability during treatment of these other problems as well. Evans et al. (1987) (90) reported reduced affective lability, as well as cognitive improvements, in a young man treated with methylphenidate or dextroamphetamine during a single-case, double-blind, placebo-controlled, dose-response study. Gualtieri et al. (1989) (97) describe sustained reduction of agitation and aggression, decreased distractibility, and improvement in affective stability among 19 of 30 TBI patients taking amantadine 50 to 400 mg/day (average dose of 290 mg/day). Udaka et al. (1984) (88) also report reductions of pathologic laughing and crying in response to amantadine or levodopa in approximately 50% of stroke or TBI patients. When patients present with affective lability or PLC in addition to cognitive and/or motivational impairments, methylphenidate, dextroamphetamine, amantadine, or levodopa may offer some relief from all of these problems.

### *Other Agents for Affective Lability*

In the event that the first-line therapies (i.e., serotonergically and/or dopaminergically active agents) do not provide adequate relief from affective lability following TBI, particularly if affective lability is comorbid with post-traumatic aggression, treatment with “mood stabilizing” (or, more appropriately in this context, “affect stabilizing”) agents may be necessary and of some benefit. Glenn et al. (1989) (98) describe an open-label trial of lithium carbonate for the treatment of affective instability and aggressive behavior in 10 patients (8 TBI and 2 stroke). The patients’ symptoms included episodic aggressive or self-destructive behavior, “mood swings,” tearfulness, and euphoria. Six of these patients demonstrated marked or moderate improvement in these target symptoms, one improved transiently, one failed to respond, and two



patients worsened with this treatment. Three patients were on concomitant neuroleptic therapy and experienced neurotoxic side effects that prompted discontinuation of the lithium. Additionally, one patient experienced decreased attentiveness and one patient experienced a seizure during this treatment. Lithium levels associated with clinical improvement ranged between 0.5–1.4 mEq/L.

Lewin and Sumners (1992) (99) describe a single case report of carbamazepine treatment of posttraumatic “episodic dyscontrol,” a term used in their report to denote uncontrolled disproportionate episodic violence, depression, and tearfulness, as well as irritability towards and intolerance of others. Treatment with carbamazepine 200 mg/day produced a good response, with no violent outbursts over the 12-month period of observation.

These reports suggest possible benefits of either lithium or carbamazepine for the treatment of some forms of affective lability following TBI, particularly in the setting of prominent episodic irritability and/or aggression. However, and as noted before, a cautious approach to dosing and continuous reassessment of benefit and adverse effects is needed in this population when using such agents.

### **Anxiety Disorders and Post-Traumatic Stress Disorder**

Anxiety disorders, including generalized anxiety disorder, panic disorder, phobias, obsessive-compulsive disorder, and/or post-traumatic stress disorder, may develop following TBI and may be a source of substantial morbidity for persons with these problems. When any of these conditions are present, clinicians should carefully assess patients for other comorbid DSM-IV Axis I or II conditions (100) that may be driving the anxiety symptoms, most notably depression, and treat these other conditions before specifically targeting anxiety symptoms. When no other comorbid neuropsychiatric condition is present, treatment should of course primarily focus on the anxiety symptoms.

Although the treatment of anxiety disorders following TBI may require medications, we generally prefer to treat complaints of anxiety in brain injury patients with supportive psychotherapy and social interventions before adding an anxiolytic medication. However, when anxiety symptoms are so severe that they require pharmacological intervention, treatment with SSRIs, benzodiazepines, or buspirone may need to be considered. There are no published reports describing the treatment of anxiety disorders following TBI. Consequently, the recommendations offered here are derived from our clinical experience and are at best preliminary.

#### *Selective Serotonin Reuptake Inhibitors*

We prefer SSRIs for the treatment of anxiety disorders following TBI given their considerable benefits on a host of

anxiety disorders in the general psychiatric population and also their relatively favorable efficacy and tolerability for other neuropsychiatric consequences of TBI. As noted earlier, the pharmacologic profiles of sertraline and escitalopram, as well as their well established efficacy in the treatment of anxiety disorders in non-brain injured persons, make these agents particularly attractive anxiolytics in this context. Since fluoxetine is associated with increased anxiety even among non-brain injured persons, it may not be the best agent with which to treat anxiety following TBI. Additionally, and as reviewed earlier in this chapter, the anticholinergic effects of paroxetine limit our enthusiasm for its use in this population despite its purported anxiolytic benefits in the general psychiatric population.

#### *Benzodiazepines*

When SSRIs fail to produce adequate and sustained anxiolysis, it may be necessary to consider treatment with a benzodiazepine or buspirone. Although benzodiazepines offer the benefit of rapid anxiolysis, their use among persons with TBI is concerning given their tendency to produce a variety of potentially problematic side effects. These agents predictably produce sedation and impair memory (101–103) even at therapeutic doses. Problems with balance, ataxia, and coordination that occur subsequent to brain injury are likely to be exacerbated by benzodiazepines. Walburga et al. (1992) (104) examined the effects of anxiolytic medications (buspirone and diazepam) on driving performance of outpatients with generalized anxiety disorder who had no neurological impairment. Each week, subjects were tested for driving ability by a 100-kilometer on-the-road driving test. Subjects who received diazepam demonstrated significantly impaired performance in the first, second, and third weeks. No impairment was detected in the subjects who received buspirone. The likelihood of similar or worse effects among TBI patients is not trivial, and poses serious concerns with respect to the effect of benzodiazepines on both everyday function and potentially risky endeavors such as driving or operating heavy machinery. Finally, in light of the fact that TBI is not uncommonly associated with pre-injury alcohol and/or drug problems, prescribing benzodiazepines for these patients may carry risks of not only dependence to these agents but also additional morbidity among those at risk for relapsing into alcohol abuse/dependence.

This constellation of adverse effects that make the use of benzodiazepines for the treatment of anxiety in patients with brain injury undesirable, and their use as first-line treatments for anxiety following TBI is not encouraged. When these agents are used, agents with moderate half-lives (lorazepam, oxazepam) are preferable to those with very short half-lives (which are highly

reinforcing and may produce rebound anxiety between doses) or very long half-lives (which may result in cumulative adverse effects with repeated administrations).

### *Buspirone*

Gualtieri (105, 106) observed “decreased anxiety, depression, irritability, somatic preoccupation, inattention, and distractibility” among four of seven patients with “post-concussion syndrome” during treatment with buspirone. As noted above, buspirone appears to carry less risk of worsening cognitive functioning in patients with TBI than benzodiazepines (104), and use of buspirone is not associated with dependency to this medication. As such, buspirone may be useful as a treatment for anxiety following TBI.

When used for this purpose, starting doses of buspirone are generally in the 5 mg BID to TID range. Gradual increases to as much as 15 mg TID are not uncommon. Side effects from buspirone include dizziness, lightheadedness, and (in rare cases) paradoxically increased anxiety. Unfortunately, buspirone’s therapeutic effects appear to require several weeks to develop. This prolonged latency of action sometimes necessitates short-term treatment with another anxiolytic, usually one of the benzodiazepines, and/or more intensive psychotherapy in order to keep the patient engaged in the use of this medication.

### **APATHY**

States of diminished motivation, or apathy, are common consequences of traumatic brain injury (18). It is important to be clear that in this context the term diminished motivation does not carry the connotation of “poor effort” or malingering that is sometimes associated with the use of this term in medicolegal contexts. Instead, the terms diminished motivation and apathy are used here to denote a neuropsychiatric syndrome in which there is a clinically significant decrease in goal-directed cognition, emotion, and/or behavior (107). Each of these three elements of the apathy syndrome may be present in varying degrees in individual patients; when present to any degree, they may interfere with rehabilitation efforts and functioning in everyday life (108). Apathetic states occur on a continuum of severity, with states of mildly diminished motivation at one end that continuum and akinetic mutism at the other end.

Although diminished motivation may be a feature of other neuropsychiatric conditions (109), and most notably depression, the syndrome of apathy also occurs independently of these conditions (110). Kant et al. (1998) (111) examined the prevalence of apathy in 83 consecutive persons with TBI seen in a neuropsychiatric clinic. Approximately 11% demonstrated apathy without depression, and an equal number were depressed

without apathy. An additional 60% of patients exhibited both apathy and depression. These authors report that younger patients, and also patients with more severe injuries, were more likely to be apathetic than older patients, among who combined symptoms of depression and apathy were more common.

Apathetic states tend to arise in the setting of significant and usually bifrontal injuries involving the anterior cingulate cortex (18), and are associated with other cognitive impairments related to frontal lobe function. Andersson and Bergedalen (2002) (112) used the Apathy Evaluation Scale (AES) (5) and a comprehensive neuropsychological assessment to ascertain the associations between cognition and apathy in 53 patients with severe TBI. They observed significant correlations between apathy score and reduced performance on tests of acquisition and memory, psychomotor speed, and executive functions. Accordingly, the treatment of these cognitive functions may improve motivation (see Chapter 53) or conversely the treatment of apathy may improve frontally-mediated cognition.

Determining whether an individual patient’s apathy is a symptom of another neuropsychiatric condition such as depression or is instead an independent syndrome is imperative prior to undertaking treatment. When apathy is a feature of depression, treatment of the underlying depression with agents like the SSRIs may relieve both mood and apathy symptoms. However, when apathy occurs as an independent problem the SSRIs are unlikely to improve this problem and may actually worsen it (113). Complicating matters, apathy not uncommonly co-occurs with behavioral dyscontrol (i.e., disinhibition, impulsivity, and aggression). This seemingly odd combination of behavioral problems may occur in the setting of injury to both the anterior cingulate-subcortical circuits (resulting in apathy) and lateral orbitofrontal-subcortical circuits (resulting in a behavioral dyscontrol syndrome). In such circumstances, patients appear apathetic at baseline and demonstrate episodic behavioral dyscontrol when an environmental or somatic stimulus produces automatic (and often aggressive or appetitive) behaviors. The development of the latter may be simplistically understood as reflecting a response to environmental or somatic stimuli sufficient to activate limbic-subcortical circuits involved in appetitive or aggressive behaviors despite a relative lack of motivation for behavioral responses more generally. This combination of apathy and behavioral dyscontrol presents substantial challenges to clinicians attempting to treat such problems, as the therapies to improve apathy may worsen behavioral dyscontrol and the therapies for behavioral dyscontrol may worsen apathy. If clinicians select apathy as the target of treatment, psychostimulants and other dopaminergically active medications are the principal pharmacotherapies (114).

### *Amantadine*

Among these pharmacotherapies for posttraumatic apathy, amantadine is most often used. Kraus and Maki (1997) (115) report on the use of amantadine among seven patients with the apathy syndrome (6 with TBI, 1 with meningitis following sinus surgery). All patients showed some degree of positive response behaviorally and cognitively during treatment, and only one experience intolerable side effects; importantly, these side effects resolved upon discontinuation of the medication. Van Reekum et al. (1995) (116) describe a single-case, double-blind, placebo-controlled study of amantadine 100 mg TID for the treatment of apathy following TBI. In that study, therapists and nurses completed inventories scoring efforts towards initiation of therapeutic activities during each session, progress in therapy, and participation in therapy during four treatment periods (two active medication, two placebo) of 2 weeks duration each. They report marked improvement in apathy, although not restoration of normal initiation, during both active treatment periods and also observed no significant treatment-emergent side effects. Amantadine also may be beneficial in the treatment of posttraumatic anergia, abulia, mutism, anhedonia, and perseveration (97, 117, 118).

Amantadine is often started at doses of 50–100 mg BID, and increased every week by 100 mg/day to either symptomatic improvement or medication intolerance. In the experience of the authors, amantadine 100 mg BID is often sufficient to impart maximal benefit without undue side effects. When higher doses are necessary, the maximum dosage of amantadine should not exceed 400 mg/day. Headache, nausea, diarrhea, constipation, anorexia, dizziness, lightheadedness, orthostatic hypotension, anxiety, irritability, depression, and hallucinations may occur during treatment with amantadine, although these latter neuropsychiatric side effects are relatively uncommon. At higher doses, psychosis and confusion may occur and may reflect the relatively robust NMDA receptor antagonism when administered at such doses. Additionally, coadministration of triamterene/hydrochlorothiazide may decrease renal excretion of amantadine, resulting in medication intolerance at otherwise therapeutic doses. These adverse reactions tend to occur more often in elderly patients than in younger patients.

Although amantadine does not possess direct anticholinergic activity *per se* at conventional therapeutic doses, it is not uncommon for patients treated with this agent to develop anticholinergic-like symptoms. Additionally, amantadine may potentiate the effects of anticholinergic agents and other psychostimulants. These observations leave open the question of amantadine on cholinergic function *in vivo*, as the direct receptor effects of this agent would not predict these effects.

It has been reported that amantadine may lower seizure threshold (97). The pharmacology of amantadine, and particularly its NMDA receptor antagonist properties, would not predict this effect. Indeed, the suggestion that amantadine reduces seizure threshold is not well supported by the literature. To the contrary, amantadine has been suggested as an augmentation strategy for the treatment of refractory epilepsy in adults (118) and children (119). In the study by Drake et al. (1991) (119), amantadine (titrated to 400 mg/day) was added to the ongoing anticonvulsant regimen of ten patients with refractory epilepsy in the setting of mental retardation. During treatment with amantadine, seizure frequency was reduced by greater than 90% in two patients, reduced by 50–90% in two patients, unchanged in three patients, and worsened in three others. In the study by Shields et al. (1985) (120), ten children with medically refractory seizures on anticonvulsant medications were treated adjunctively with amantadine. Of these, one experienced improvement in tonic seizures, one worsened, and the others remained unchanged. These reports suggest that when looked at as a group, patients with epilepsy do not invariably experience significant changes in seizure frequency during treatment with amantadine. Individual patients may experience improvements, worsening, or no change in seizure frequency during treatment with this medication. These studies suggest that patients with TBI, including those with posttraumatic seizures, may not be precluded from treatment with amantadine; however, careful monitoring for change in seizure activity or the development of new-onset seizures during treatment with this agent is recommended.

### *Bromocriptine*

Bromocriptine has also been used in the treatment of diminished motivation following TBI or subarachnoid hemorrhage (121). In this study, bromocriptine was used in an open-label fashion in six men and five women two months to five years post-injury. The authors of this study report that bromocriptine improved scores on measures of motivation and cognition, but not mood, and that improvement was maintained after bromocriptine was withdrawn in eight of the patients. The mechanism by which sustained benefit was achieved by this treatment is not clear. Eames (1989) (122) also suggested that bromocriptine and/or L-dopa/carbidopa may be useful in treating cognitive initiation problems among persons with brain injury who are at least 1 year post-injury. In a related area, Catsman-Berrevoets and Harskamp (1988) (123) observed improvements in motivation in a patient with bilateral thalamic stroke. These studies suggest that bromocriptine may be of some use in the treatment of apathy in brain-injured persons, including those with TBI.

Treatment with bromocriptine generally begins with 2.5 mg/day and is gradually titrated to the highest dose tolerated. Common side effects during treatment with bromocriptine include dizziness, drowsiness, faintness, syncope, nausea, vomiting, abdominal cramps, constipation, and diarrhea, although these are generally of mild severity. Uncontrolled hypertension and hypersensitivity to ergot alkaloids are strict contraindications to the use of bromocriptine. Although use of this agent among women who are breastfeeding their infants is contraindicated, use during pregnancy does not appear to be associated with significant increased adverse events or outcomes on fetal development. Additionally, it has been suggested that bromocriptine may possess some anticonvulsant properties (124). Although this suggestion should not be misunderstood as an endorsement of bromocriptine for the adjunctive treatment of posttraumatic epilepsy, it may offer some reassurance of its safety for use among cognitively impaired TBI survivors with this additional posttraumatic problem.

#### *L-Dopa/Carbidopa*

Lal et al. (1988) (125) reported on the use of L-dopa/carbidopa among 12 patients with brain injury, including several patients with hypoxic-ischemic brain injuries. During treatment with L-dopa/carbidopa 10/100 to 25/250 QID, patients demonstrated improvements in alertness and concentration, decreased fatigue, hypomania, and sialorrhea, and improved memory, mobility, posture, and speech. Whether fatigue in this sample is a symptomatic equivalent to apathy is not clear. DeBette et al. (2002) (126) used a levodopa/benserazide combination in five patients with cognitive, emotional, and neurobehavioral disturbances following hypoxic-ischemic brain injury. They describe variable improvements in these neuropsychiatric symptom domains during treatment, and particularly on motor dysfunction and apathy; improvements in cognition were relatively more modest. Although L-dopa/carbidopa is uncommonly used in clinical practice for the treatment of apathy, in some cases it may be an alternative to amantadine or the other catecholaminergically active agents when these have produced intolerable side effects.

#### *Methylphenidate and Dextroamphetamine*

Psychostimulants, such as methylphenidate and dextroamphetamine also may be useful for the treatment of apathy in cases in which diminished arousal, slowed speed of cognitive processing, and attentional impairments are prominent (90, 127, 128). However, these agents are not generally regarded as first-line treatments for apathy alone. This issue is discussed in more detail in Chapter 53 (Pharmacotherapy of Cognitive Impairments).

#### *Other Agents*

Cummings (2000) (129) and Levy et al. (1999) (130) suggest that the cholinesterase inhibitors (donepezil, rivastigmine, galantamine) may be of benefit for neuropsychiatric disturbances, including apathy, in persons with dementing illnesses such as Alzheimer's disease and dementia with Lewy bodies. In light of the cholinergic deficits produced by TBI and the growing use of these agents for the treatment of impaired cognition following TBI (see Chapter 53), these agents may be of similar behavioral benefit for persons with posttraumatic apathy. However, there is at present no data to support this suggestion, and the use of these agents for this purpose alone is not at present recommended.

Protriptyline, a secondary amine tricyclic agent, has been suggested to have sufficient stimulant properties to permit its use for anergia and diminished motivation in TBI patients (131). Interestingly, despite its ability to improve arousal and motivation, it does not appear to confer additional benefits on cognition. Whether this reflects the effects of this agent's anticholinergic properties or not is at present uncertain. Similarly, Reinhard and colleagues (1996) (132) administered amitriptyline (1 patient) and desipramine (2 patients) and found improvement in arousal and initiation after TBI, which they hypothesized resulted from the pro-noradrenergic effects of these agents. Although TCA's may be of some benefit for apathy following TBI, they are probably best regarded as treatments of last resort for this purpose.

#### *Psychosis*

##### *Typical Antipsychotics*

Although typical antipsychotic medications have been used to control agitation and psychosis following TBI, these are not benign treatments in this population. Stanislav (1997) (133) demonstrated improvement in cognitive performance in brain-injured patients following discontinuation of typical antipsychotic medications, the magnitude of which appeared to be greater after discontinuation with thioridazine than haloperidol. While both medications appeared to negatively affect cognitive performance, Stanislav (1997) (133) suggests that the greater improvement observed after discontinuation with thioridazine is attributable to the brain-injured patients' reduced tolerance to the anticholinergic properties of this agent. Similarly, Sandel et al. (1993) (134) observed new-onset delusions in a TBI patient receiving chlorpromazine for the treatment of agitation following TBI, an effect that may also be attributable to the significant anticholinergic properties of this agent. Antipsychotic medications have also been reported to delay neuronal recovery after brain injury (135). Consistent with this observation,

Rao et al. (1985) (136) found that patients treated with haloperidol in the acute period following TBI experienced significantly longer periods of posttraumatic amnesia than patients not treated with this medication. However, this delay in emergence from posttraumatic amnesia did not result in difference in functional outcome following acute rehabilitation.

Side effects during treatment with typical antipsychotic agents include hypotension, sedation, and confusion, and are not uncommon. Patients with brain injury are particularly subject to dystonias, akathisias, and other parkinsonian side effects — even when relatively low doses of antipsychotic medications are prescribed (138). Consistent with their greater sensitivity to medications affecting the central nervous system, patients with brain injury are more sensitive to the development of extrapyramidal symptoms during treatment with typical antipsychotic medications (137–141). Given this literature and the availability of several atypical antipsychotic medications, the authors strongly discourage the use of typical, and particularly the low-potency, typical antipsychotics among persons with TBI.

#### *Atypical Antipsychotics*

There is at present a dearth of reports to guide selection among the atypical antipsychotic agents in this population. Michals et al. (1993) (142) used clozapine (Clozaril) to treat nine brain-injured patients with psychotic symptoms or outbursts of rage and aggression that had failed to respond to other medications. Three of these patients demonstrated marked improvements in aggression and/or psychosis, three demonstrated decreased agitation and auditory hallucinations, and an adequate duration of treatment was not achieved in three patients. Two of these nine patients experienced seizures during treatment. Burke et al. (1999) (143) also report improvement in refractory psychotic symptoms after TBI during treatment with clozapine. These reports suggest that clozapine may be useful in the treatment of psychosis and aggressive behavior after brain injury. Unfortunately, this treatment carries a relatively high risk of adverse effects including seizures and agranulocytosis. Additionally, the laboratory monitoring protocol required during its use is for many clinicians and patients too cumbersome to be practical. Whether clozapine may also exacerbate cognitive impairments given its substantial anticholinergic properties is not clear, but seems likely in light of such effects produced during treatment with other low-potency antipsychotic agents.

Schreiber et al. (1998) (144) report a case in which risperidone treated delusions and sleep disturbance following TBI effectively. One of the authors (DA) has used this medication in two patients that developed psychosis (paranoid delusions, auditory hallucinations) after TBI in the acute rehabilitation setting. Each patient responded

with decreasing psychotic symptoms with risperidone 4 mg per day and without significant adverse effect. The second of these patients was treated in an A-B-A-B fashion, and psychosis recurred during each reduction of risperidone below 3 mg per day. There are, to-date, no studies reporting improvement in psychosis following TBI during treatment with olanzapine, quetiapine, or ziprasidone. Each of these medications may be of benefit in this population, but specific benefits and side effect profiles relevant to their use in TBI remain to be determined. Based on the literature and our own clinical experience in this area, we recommend either risperidone or olanzapine as first-line for the treatment of psychosis following TBI. Starting doses of risperidone are 0.5 mg Qhs or BID, and may be increased in 0.5–1 mg increments up to 4–6 mg/day. Beyond this level, additional increases in dose are associated with extrapyramidal side effects and a more “typical” antipsychotic side effect profile. Starting doses of olanzapine are 2.5–5 mg Qhs or BID, and may be increased in 2.5–5 mg increments up to 20 mg/day.

#### *Special Consideration in the Use of Antipsychotic Agents*

Neuroleptic malignant syndrome is a potentially life-threatening disorder that may emerge during the use of any antipsychotic agent. This syndrome has been reported among patients receiving haloperidol after TBI (139, 145). Patients experiencing neuroleptic malignant syndrome become severely rigid and occasionally catatonic. There is fever, elevated white blood cell count, tachycardia, abnormal blood pressure fluctuations, tachypnea, and diaphoresis. Although medications such as bromocriptine and dantrolene sodium have been suggested as treatments for neuroleptic malignant syndrome, the most important therapeutic interventions are discontinuation of antipsychotic medications, treatment of any underlying infections or other concurrent medical illnesses, and symptomatic treatment of fever and hypertension (146).

Many psychotropic medications affect seizure threshold. This is of particular concern in this population given the risk of seizures after TBI. Among all the first-generation antipsychotic drugs, molindone and fluphenazine have consistently demonstrated the lowest potential for lowering the seizure threshold (68, 147). Clozapine treatment is associated with a significant dose-related incidence of seizures (ranging from 1% to 2% of patients who receive doses below 300 mg/day, and 5% of patients who receive 600–900 mg/day) (148). The observations of Michals et al. (1993) (142) suggest that this risk may be increased in patients with TBI receiving clozapine. If this agent is prescribed at all in these patients, its use should be undertaken with extreme caution and only for the relief of refractory psychotic symptoms.

## AGGRESSION AND AGITATION

Aggressive and/or agitated behavior is a major source of disability to individuals with brain injury and a major source of stress to families of persons with this problem. Additionally, these behaviors can endanger the safety of not only patients and their families but also the professionals providing care to them. A multimodal, multidisciplinary, collaborative approach to treatment is necessary in most cases. The concurrent use of family treatments, psychopharmacologic interventions, and psychotherapeutic approaches is often required. In establishing a treatment plan for patients with agitation or aggression, the overarching principle is that diagnosis comes before treatment. It is essential to determine the mental status of the patient before the agitated or aggressive event, the nature of the precipitant, the physical and social environment in which the behavior occurs, the ways in which the event is mitigated, and the primary and secondary gains related to agitation and aggression (149, 150).

Although there is no medication that is approved by the FDA specifically for the treatment of aggression, medications are widely used (and commonly misused) in the management of patients with acute or chronic aggression. Unfortunately, there is a paucity of rigorous double-blind, placebo controlled studies (i.e. "Level I" studies) or even prospective cohort studies (i.e. "Level II") to guide clinicians in the use of pharmacologic interventions. The International Brain Injury Association has assembled a task force on reviewing the literature on this literature pertaining to the neurobehavioral consequences of TBI (in progress). At this time, we suggest utilizing the Consensus Guidelines for the Treatment of Agitation in the Elderly with Dementia as a framework for the assessment and management of agitation and aggression after TBI (151), with the caveat that the effectiveness of these medications is highly variable in persons with TBI.

Medications for posttraumatic aggression and/or agitation are generally selected with one or another hypothesis in mind regarding the neurochemistry of these problems. For example, hypothesized strategies for treatment of aggression and agitation include inhibition of excessive activity in temporolimbic areas with anticonvulsants, reduction of "hyperactive" limbic monoaminergic neurotransmission with  $\beta$ -adrenergic receptor antagonists (i.e., propranolol) or dopamine receptor antagonists (i.e., haloperidol), augmentation of orbitofrontal and/or dorsolateral prefrontal cortical activity with monoaminergic agonists (i.e., amantadine, methylphenidate, and perhaps bupirone), or modulation of limbic and frontal activity through augmentation of serotonergic activity (e.g., SSRIs). However, the neurochemistry of posttraumatic aggression is not well understood and may differ between individuals. Consequently, the pharmacologic treatment

of this problem often entails a trial-and-error approach to find a medication that is both effective and tolerable.

After appropriate assessment of possible etiologies of these behaviors, treatment is focused on the occurrence of comorbid neuropsychiatric conditions (depression, psychosis, insomnia, anxiety, delirium). When present, aggression or agitation may be a manifestation of these problems rather than an independent diagnosis. Therefore, comorbid neuropsychiatric conditions should be treated prior to developing an independent treatment approach to the patient's agitation or aggression. Additionally, it is important to consider whether the behavior is occurring in the acute (hours to days) or chronic (weeks to months) phase after TBI, and also the severity of the behavior (mild to severe). The differential diagnosis of posttraumatic aggression varies as a function of time since injury, with confusional states being more common in the early post-injury period and other neuropsychiatric problems such as psychosis being more common in the late post-injury period. The effects of these treatments may vary depending on the presence of other neuropsychiatric conditions and the time since injury. Finally, clinicians should bear in mind that patients may not respond to just one medication, but may require combination treatment, similar to the pharmacotherapeutic treatment for refractory posttraumatic depression.

### Acute Aggression

#### *Antipsychotics*

Antipsychotics are the most commonly used medications in the treatment of aggression. Although these agents are appropriate and effective when aggression arises as a result of psychosis, the use of typical antipsychotic agents to treat chronic aggression in the absence of psychosis is often ineffective and may result in serious treatment-related complications such as tardive dyskinesia. Usually, it is the sedative side effects rather than the antipsychotic properties of antipsychotics that are used (i.e., misused) to "treat" (i.e., mask) the aggression. Often, patients develop tolerance to the sedative effects of the neuroleptics and, therefore, require increasing doses. As a result, extrapyramidal and anticholinergic-related side effects occur. Paradoxically (and frequently), akathisia may result from the use of these agents and thereby worsen agitation and restlessness. As the dose of neuroleptic is increased, especially when a high-potency antipsychotic such as haloperidol is administered, these symptoms predictably worsen. Akathisia is often mistaken for increased irritability and agitation, setting in motion a cycle of increasing neuroleptics and worsening akathisia.

There is some evidence from studies of injury to motor neurons in animals that have found that haloperidol decreases recovery. This effect was only seen when animals actively participated in a behavioral task and not

when the animals were restrained after drug administration (135). It is possible that the effect on decreasing dopamine and inhibiting neuronal function, which may be the mechanism of action to treat aggression, may have other detrimental effects on recovery. As noted earlier, Rao et al. (1985) (136) found that patients treated with haloperidol in the acute period following TBI experienced significantly longer periods of posttraumatic amnesia. This finding raises important potential risk/benefit issues that must be considered before antipsychotic drugs are used to treat aggressive behavior in patients with neuronal damage.

In patients with brain injury, psychosis, and aggression, we recommend atypical antipsychotics as first-line treatments for acute agitation following TBI. Starting doses of these medications should be low (i.e., risperidone 0.5 mg) and repeated at short intervals (sometimes as frequent as every hour) until control of aggression is achieved. If after several administrations of risperidone the patient's aggressive behavior does not improve, the hourly dose may be increased until the patient is so sedated that he or she no longer exhibits agitation or violence. Once the patient is not aggressive for 48 hours, the daily dosage should be decreased gradually (i.e., by 25%/day) to ascertain whether aggressive behavior reemerges. In this case, consideration should then be made about whether it is best to increase the dose of risperidone and/or to initiate treatment with a more specific anti-aggressive medication or nonpharmacologic intervention. Other atypical antipsychotic medications such as olanzapine, quetiapine (which produces little in the way of extrapyramidal symptoms), or ziprasidone may be used, although there is no published experience with these medications in persons with TBI.

### *Benzodiazepines*

The literature regarding the effects of the benzodiazepines in the treatment of aggression is inconsistent, at best. The sedative properties of benzodiazepines are helpful in the management of acute agitation and aggression in many cases. Paradoxically, increased hostility, aggression, and the induction of rage may occur in patients treated with benzodiazepines, and particularly persons with neurological problems, although this phenomenon is rare (152). Benzodiazepines can produce amnesia, and preexisting memory dysfunction can be exacerbated by the use of benzodiazepines. Brain-injured patients may also experience increased problems with coordination and balance with benzodiazepine use. For this reason, we do not recommend the use of benzodiazepines for the treatment of acute aggression in patients with TBI.

### **Chronic Aggression**

If a patient continues to exhibit periods of agitation or aggression over weeks to months, prophylactic use of

medications may be required to decrease or prevent these behaviors. Consideration of such medications should be undertaken only after evaluation of the antecedents and consequences of these behaviors and attempts to address these issues in the service of decreasing aggression and agitation nonpharmacologically.

### *Antipsychotics*

If, after thorough clinical evaluation, it is determined that the aggressive episodes result from psychosis, such as paranoid delusions or command hallucinations, then antipsychotic medications will be the treatment of choice. There have been double-blind placebo controlled studies of risperidone showing efficacy in the treatment of agitation in elderly patients with dementia (153, 154), as well as children with autism and serious behavioral problems (155). Olanzapine appears to be more sedating, and quetiapine produces more limited extrapyramidal symptoms than does risperidone. Quetiapine appears to be the antipsychotic medication (except for clozapine) least likely to produce extrapyramidal effects in vulnerable populations, such as those with Parkinson's disease (156). Clozapine may have greater antiaggressive effects than other atypical antipsychotic medications (142), but its propensity to impair cognition and increase seizure risk, and as well as the arduous hematologic monitoring required during its use, may offset its potential benefits in this population. Based on the available evidence and our own clinical experience, we suggest that when atypical antipsychotics are used for post-traumatic aggression or agitation, risperidone, olanzapine, and quetiapine should be considered first-line before the other even newer atypical antipsychotic agents.

### *Buspirone*

Serotonin appears to be a key neurotransmitter in the modulation of aggressive behavior. In preliminary open case studies, buspirone, a 5-HT<sub>1A</sub> agonist, has been reported to be effective in the management of aggression and agitation for patients with head injury (105, 106, 157), as well as dementia, and developmental disabilities and autism (150). In rare instances, we have found that some patients become more aggressive when treated with buspirone. We recommend that buspirone be initiated at low dosages (i.e., 5 mg BID) and increased to 10 mg BID after one week. Dosages of 45–60 mg/day may be required before there is improvement in aggressive behavior, although we have sometimes observed dramatic improvement within one week of treatment initiation.

### *Benzodiazepines*

Clonazepam may be effective in the long-term management of aggression, although evidence is restricted to case

reports. Freinhar and Alvarez (1986) (159) found that clonazepam decreased agitation in three elderly patients with organic brain syndromes. Keats and Mukherjee (1988) (160) reported anti-aggressive effects of clonazepam in a patient with schizophrenia and seizures. We use clonazepam when pronounced aggression and anxiety occur together, or when aggression occurs in association with neurologically-induced tics and similarly disinhibited motor behaviors. Doses should be initiated at 0.5 mg BID and may be increased to as high as 2–4 mg BID, as tolerated. Unfortunately, sedation and ataxia are frequent side effects during treatment with this agent among persons with TBI. As noted earlier, the risk:benefit ratio of benzodiazepine use in this population should be given serious consideration prior to initiating treatment with these agents.

### *Anticonvulsants*

Carbamazepine has been shown to be effective for the treatment of idiopathic bipolar disorder and has also been advocated for the control of aggression in both epileptic and nonepileptic populations. Open-label studies have indicated that carbamazepine may be effective in decreasing aggressive behavior associated with developmental disabilities, schizophrenia, and patients with a variety of other organic brain disorders (150). Several of these studies included individuals with TBI. Chatham-Showalter (1996) (161) observed improvement in seven TBI patients treated in an open-label fashion with carbamazepine, and observed these improvements after only four days of treatment. In an open-label study of carbamazepine on assaultive behavior in eight patients with “organic brain diseases” (only two had brain injury from gunshot wounds), Patterson (1987) (162) reported that the number of episodes decreased by over 50% as documented by nursing staff. In a study by Azouvi and coworkers (1999) (163), ten patients presenting with agitation and anger outbursts after severe TBI experienced significant reduction in such behaviors as assessed using six relevant items on the Neurobehavioral Rating Scale-Revised (164) during 8 weeks of treatment with carbamazepine (mean dose of  $9.47 \pm 2.9$  mg/kg/day). However, four of the ten patients experienced significant drowsiness during the course of the study, necessitating use of lower doses than had been initially planned and that may thereby have reduced the effectiveness of this treatment. An additional patient developed a significant allergic cutaneous reaction necessitating discontinuation of carbamazepine. While the authors of this study report no significant changes in cognition during the course of this trial, their primary measure of cognition was the Mini-Mental State Examination – a measure which is widely regarded as a poor instrument for the assessment of cognition following traumatic brain injury due to its insensitivity to executive

dysfunction and to impairments of the speed and efficiency of information processing. Hence, a failure to find no change in cognition in this study must be regarded with some caution since the measure used is unlikely to be sensitive to such changes in persons with TBI.

In our experience and that of others, the anticonvulsant valproic acid may also be helpful to some patients with organically induced aggression (165–167), although there are only a few open-label case reports regarding the use of this agent among persons with aggression following TBI. Horne and Lindley (1995) (168) report a case of a 70 year-old woman whose posttraumatic emotional lability and irritability improved during treatment with valproate. Wroblewski et al. (1997) (169) observed significantly reduced posttraumatic aggression among five individuals, and report that those improvements occurred within 1–2 weeks of treatment initiation.

Gabapentin may be beneficial for the treatment of agitation in patients with dementia (170, 171). Doses have ranged from 200–2400 mg/day. However, Childers and Holland (1997) (172) report an increase in anxiety and restlessness (i.e., agitation) in two cognitively impaired TBI patients for whom gabapentin was used primarily to reduce chronic pain. Although this report is not consistent with our use of this agent among persons with TBI, it is unclear whether or to what extent gabapentin is of benefit for the treatment of posttraumatic agitation and/or aggression.

For patients with aggression and epilepsy whose seizures are being treated with anticonvulsant drugs such as phenytoin and phenobarbital, switching to carbamazepine or to valproic acid may treat both conditions and reduce adverse side effects (i.e., sedation, confusion, disinhibition) that is sometimes seen in persons treated with the older anticonvulsants such as phenobarbital. Oxcarbazepine may be an alternative to carbamazepine in light of its relative lack of hepatic autoinduction, more favorable drug-drug interaction profile, and more limited cognitive and motor effects, but there are no published reports of its use among persons with aggression following TBI at the time of this writing.

### *Lithium*

Although lithium is known to be effective in controlling aggression related to manic excitement, many studies suggest that it may also have a role in the treatment of aggression in selected, nonbipolar patient populations. These include patients with mental retardation who exhibit self-injurious or aggressive behavior, children and adolescents with behavioral disorders, prison inmates, and those with other organic brain syndromes (150). Two individuals in state psychiatric facilities with brain-injury related aggression (one patient with TBI and one with post-anoxic encephalopathy) responded to an open-label trial of



lithium (173). Glenn and colleagues (1989) (98) reported their experience using lithium in the treatment of ten "brain-injured patients with severe, unremitting, aggressive, combative, or self destructive behavior or severe affective instability." Five patients had a "dramatic response."

As noted earlier, individuals with brain injury have increased sensitivity to the neurotoxic effects of lithium (174, 175). Because of lithium's potential for neurotoxicity, we limit the use of lithium in those patients whose aggression is related to manic effects or recurrent irritability related to cyclic mood disorders.

### *Antidepressants*

The antidepressants that have been reported to control aggressive behavior include those that act preferentially (amitriptyline) or specifically (trazodone, sertraline, and fluoxetine) on serotonin. In open studies, Mysiw et al. (1988) (176) and Jackson et al. (1985) (177) reported that amitriptyline (maximum dose 150 mg/day) was effective in the treatment of twenty patients with recent severe brain injury whose agitation had not responded to behavioral techniques. Improvement was documented in 12/17 patients within the first week of treatment. Szlabowicz and Stewart (1990) (178) successfully treated a 43-year-old man with aggressive behavior subsequent to anoxic encephalopathy with amitriptyline 75 mg Qhs. Trazodone has also been reported to be effective in the treatment of aggression that occurs with organic mental disorders (150). As noted earlier in this chapter, Kant et al. (1998) (18) conducted an open-label 8-week open trial of sertraline in 13 patients with irritability and aggression after TBI. Behaviors were monitored using the Overt Aggression Scale-Modified for outpatients, and sertraline was administered up to 200 mg/day. This treatment produced a significant reduction in irritability and aggression.

Fluoxetine, a potent serotonergic antidepressant, has been reported to be effective in the treatment of aggressive behavior in a patient who suffered brain injury as well as in patients with personality disorders and depression, and adolescents with mental retardation and self-injurious behavior (150). We have used selective serotonin reuptake inhibitors with considerable success in aggressive patients with brain lesions. The dosages used are similar to those for the treatment of mood lability and depression, and should be guided by the ease-of-use considerations discussed in the preceding sections of this chapter.

### *Stimulants*

There have been several studies that have examined the role of dopaminergic medications and stimulants in the treatment of agitation and aggression. Nickels et al. (1994) (118) report improvement during treatment with amantadine in two of three subjects with post-coma

agitation, and Chandler et al. (1988) (117) report improvement during treatment with amantadine in two patients with agitation and aggression in the post-acute injury period. Mooney and Haas (1993) (179) conducted a randomized, pretest, posttest, placebo-controlled, single-blind study of the effect of methylphenidate 30 mg/day for six weeks on brain injury related anger in 38 individuals with "serious" TBI occurring six or more months prior to treatment. Patients treated with methylphenidate had a lower level of anger. Although we do not recommend these agents as first-line treatments for agitation or aggression following TBI, they should be considered in patients in who there is evidence from neuroimaging of sufficient remaining frontal cortex to permit these agents to augment function in that area and restore its ability to inhibit or modulate limbically-mediated behaviors. In the absence of remaining frontal cortex, these agents pose the risk of further increasing limbic drive and worsening agitated or aggressive behavior.

### *$\beta$ -Adrenergic Receptor Antagonists*

Since the first report of the use of  $\beta$ -adrenergic receptor antagonists (" $\beta$ -blockers") in the treatment of acute aggression in 1977, over 25 articles describing the use of  $\beta$ -blockers with over 200 patients with aggression have appeared in the neurologic and psychiatric literature (150). Most of these patients had been unsuccessfully treated with antipsychotics, minor tranquilizers, lithium, and/or anticonvulsants before treatment with  $\beta$ -blockers. The agents in this medication class that have been investigated in controlled prospective studies include propranolol (a lipid-soluble, nonselective  $\beta$ -adrenergic receptor antagonist), nadolol (a water-soluble, nonselective  $\beta$ -adrenergic receptor antagonist), and pindolol (a lipid-soluble, nonselective  $\beta$ -adrenergic receptor antagonist with partial sympathomimetic activity).

The effectiveness of propranolol in reducing agitation has been demonstrated during the initial hospitalization after TBI in a double-blind placebo-controlled study in 21 subjects with severe TBI (180). The maximum intensity of episodes and the numbers of episodes were less after propranolol than they were after placebo as assessed using the Overt Aggression Scale. Unfortunately, the authors of this study do not list the number of patients who dropped out at each time point during the study, thus diminishing the reliability of the conclusions. Greendyke and colleagues (1986) (181) performed a double-blind randomized placebo-controlled crossover study of propranolol in ten patients with aggression (mean dose 520 mg/day). Only 5 patients had TBI, and the response of these patients varied. These authors later performed a double-blind randomized placebo-controlled crossover study of pindolol (doses up to 60 mg/day) in 11 patients with behavioral problems, including aggression (182). It

appears that most of these patients also participated in their earlier propranolol study, and again only five of these were patients with TBI. Although the patients as a group demonstrated improvement in assaultiveness, hostility, and uncooperativeness, we are unable to assess whether the TBI patients responded differentially. Alpert and colleagues (1990) (183) used nadolol in chronically hospitalized patients with aggression, and observed improvements in this symptom during treatment with this agent. Unfortunately, these patients did not have TBI.

Collectively, the literature suggests that  $\beta$ -adrenergic receptor antagonists are effective agents for the treatment of aggressive and violent behaviors, particularly those related to "organic brain syndromes" such as TBI. Patients with reactive airway disease (asthma), chronic obstructive pulmonary disease, insulin-dependent diabetes mellitus, congestive heart failure, persistent angina, significant peripheral vascular disease, and hyperthyroidism are not good candidates for treatment with  $\beta$ -blockers. Among patients without cardiovascular or cardiopulmonary problems, propranolol may be initiated at doses of 60 mg/day and increased by this amount every 3 days. Among patients with hypotension or bradycardia, treatment is usually initiated with a single test-dose of 20 mg/day and treatment should not proceed if patients develop symptoms related to these problems, if severe dizziness, ataxia, or wheezing occurs, and/or if the pulse rate is reduced below 50 beats per minute or systolic blood pressure is less than 90 mmHg. When this initial test dose is tolerated, doses of propranolol are gradually increased to 12 mg/kg body weight or until aggressive behavior is under control. Doses of 800 mg or less of propranolol are usually sufficient to control aggressive behavior. Patients should be maintained on the highest tolerable dose of propranolol for at least 8 weeks before concluding that the patient is not responding to this medication.

Given the potential for drug-drug interactions with propranolol, plasma levels of all antipsychotic and anti-convulsive medications should be monitored during treatment. In particular, propranolol is associated with significant increases in plasma levels of thioridazine, and the combination of these two medications should be avoided. When a patient requires the use of a once-a-day medication because of compliance difficulties, long-acting propranolol or nadolol may be of use. When patients develop bradycardia that prevents prescribing therapeutic dosages of propranolol, pindolol can be substituted, using one-tenth the dosage of propranolol. Pindolol's intrinsic sympathomimetic activity stimulates the  $\beta$ -adrenergic receptor and may limit the development of symptomatic bradycardia.

As suggested above, the major side effects of  $\beta$ -blockers when used to treat aggression are a lowering of blood pressure and pulse rate. Because peripheral  $\beta$ -adrenergic receptors are fully blocked in doses of

300–400 mg/day, further changes in these vital signs usually do not occur even when doses are increased beyond those levels. Despite reports of depression with the use of  $\beta$ -blockers, controlled trials and our experience indicate that it is a rare occurrence.

## SLEEP

Evaluation of sleep disturbances following TBI should first include assessment of other neuropsychiatric problems (e.g., depression, mania, anxiety, delirium) that may better account for the sleep disturbance. Independent of these problems, TBI may result in significant sleep disturbances including impaired rapid-eye-movement (REM) recovery and multiple nocturnal awakenings (184). Hypersomnia that occurs after severe penetrating head injury most often resolves within the first year after injury, whereas insomnia that occurs in patients with long periods of coma and diffuse injury has a more chronic course (185). Barbiturates and long-acting benzodiazepines should probably be avoided in this population, and if they are prescribed at all then they such should be used with great caution. These drugs interfere with REM and stage 4 sleep patterns, and may contribute to persistent insomnia (186). Clinicians should warn patients of the dangers of using over-the-counter preparations for sleeping and for colds because of the prominent anticholinergic side effects of these agents.

Trazodone, a sedating antidepressant medication that is devoid of anticholinergic side effects, is the preferred agent for the treatment of insomnia following TBI. A dose of 50 mg should be administered initially. If this dose is ineffective, doses up to 150 mg may be prescribed. Nonpharmacological approaches should be used regardless of whether or not medications are used, and should include minimizing daytime naps, maintaining regular sleep onset times, and engaging in regular physical activity during the day.

## FATIGUE

Fatigue is a common symptom among persons with traumatic brain injury, and may occur independent of other posttraumatic neuropsychiatric disturbances. When treatment of other posttraumatic neuropsychiatric problems does not adequately improve fatigue, specific treatment of this problem may be required. Psychostimulants and amantadine are the most commonly used agents for the treatment of fatigue in persons with TBI, and may be of some benefit toward that end. In our experience, dosing of these agents similar that employed for the treatment of diminished arousal and attention is usually sufficient to treat posttraumatic fatigue. These medications may be

of particular benefit in patients with posttraumatic depression in whom fatigue persists despite improvement in mood during treatment with antidepressants.

Modafinil, a medication recently approved for the treatment of excessive daytime somnolence in patients with narcolepsy, also may have a role in treatment of post-TBI fatigue. Although the exact mechanism of action of modafinil is not clear, animal studies suggest that its promotion of wakefulness may result from an indirect, dose-dependent reduction of the release of GABA in the cerebral cortex, medial preoptic area, and posterior hypothalamus (187, 188), activation of hypocretin (orexin) neurons in the lateral hypothalamus (189), and dose-dependent increases in glutamate release in the ventrolateral and the ventromedial thalamus (190). Some combination of these mechanisms in humans may increase arousal via activation in regions critical to this purpose, either directly via glutamatergic thalamic activation, indirectly via reduction of GABA function, or through the secondary effects of lateral hypothalamic projections to regions involved in control of arousal and sleep-wake cycle (tubero-mammillary nucleus and the locus coeruleus) (191).

Studies of the effect of modafinil on fatigue and excessive sleepiness in patients with multiple sclerosis (192, 193) and Parkinson's disease (194) suggest benefit. Elovic (2000) (195) has suggested that modafinil may be of similar benefit in patients with TBI. Teitelman (2001) (196) described his use of modafinil among 10 outpatients with nonpenetrating traumatic brain injury and functionally significant excessive daytime sleepiness and in two patients with somnolence due to sedating psychiatric medications. The patients included in his report were between the ages of 42 to 72 years, all were outpatients, and were treated in an open-label fashion. Doses of modafinil ranged between 100 mg to 400 mg taken once each morning. Nine of these patients reported improvements in excessive daytime sleepiness, and some patients also reported subjective improvements in attention as well as other cognitive benefits. Although this medication was generally well tolerated, this report also describes treatment intolerance due to increased "emotional instability" in two women with brain injury complicated by multiple other medical conditions and receiving multiple additional medications. At the time of this writing there are no published clinical studies with which to evaluate the effectiveness or tolerability of modafinil for post-traumatic hypersomnolence or fatigue. If used in this population, dosages should start with 100 mg in the morning, and can be increased to up to 400 mg/day administered in either a single daily dose or two divided doses (i.e., 200 mg in the morning, and 200 mg in the afternoon). Higher doses (up to 600 mg/day) are sometimes used, but there is no evidence in any patient population that such doses offer benefit beyond that achieved with 400 mg/day.

## COLDNESS

Complaints of feeling cold, without actual alteration in body temperature, are occasionally seen in patients who have suffered brain injury. This feeling can be distressing to those who experience it. Patients may wear excessive amounts of clothing, and may adjust the thermostat in their homes to the point that other members of the family are made uncomfortable. While this is not a commonly reported symptom of traumatic brain injury (TBI), Hibbard et al. (1998) (197) report that in a sample of 331 individuals with traumatic brain injury, 27.9% complained of changes in body temperature, and 13% persistently felt cold. Eames (1997) (198), while conducting a study of the cognitive effects of vasopressin nasal spray in patients with TBI, reported that thirteen patients had the persistent feeling of coldness, despite normal sublingual temperature. All were treated with nasal vasopressin spray for one month. Eleven of these patients stopped complaining of feeling cold after one month of treatment, and one other patient had incomplete improvement in this symptom.

Silver and Anderson (1999) (199) performed a pilot study of the effects of intranasal vasopressin (DDAVP) twice daily for one month among six patients who complained of persisting coldness after brain injury. Five of the six patients had a dramatic response to DDAVP – some as soon as one week after initiating treatment – and no longer complained of feeling cold. This response persisted even after discontinuation of treatment. Patients denied any side effects from treatment with this agent. The authors of this study suggest that DDAVP may reverse physiologic effects of a relative deficit in vasopressin in the hypothalamus caused by injury to the vasopressin precursor producing cells in the anterior hypothalamus, and may thereby correct an internal temperature setpoint disrupted by the brain injury.

## OTHER ISSUES IN THE PHARMACOTHERAPY OF NEUROPSYCHIATRIC DISTURBANCES FOLLOWING TBI

There has been a bias held by patients, families, and some treatment centers against the use of medications for the treatment of neuropsychiatric disorders in patients with brain injury. The bias against the use of psychiatric medications may have several bases, including the stigma associated with mental illness and psychiatric treatment, and in some cases the patient's previous and often sub-optimal experience with psychotropic medications. Stigma may relate to the view that psychiatric symptoms are signs of weakness, indolence, or even moral decline. We have suggested that the neuropsychiatric paradigm – one that rejects the misleading demarcation between

“brain” and “mind” and emphasizes the neurobiological bases of all cognitive, emotional, and behavioral problems regardless of the relationship of such problems to brain injury – is the most useful response to such biases. Patients struggling to accept treatment in the face of old stigmas may benefit from an explanation of symptoms as the products of alterations in neurotransmitters, brain structures, brain networks, or some combination of these, and from the presentation of treatments as designed to alleviate or compensate for such brain dysfunctions.

Unfortunately, particularly for patients with TBI, the experience of treatment with psychotropic medications has often been a negative one and their biases against treatment with some of these medications are not entirely without merit. Antipsychotic medications, and particularly typical antipsychotics, are widely misused as a general “tranquilizer” to sedate patients agitated after TBI, with resulting impairment in alertness, cognition, and (in some cases) the production of severe extrapyramidal symptoms. For example, we evaluated in consultation one patient who had been treated with low-dose fluphenazine to control agitated behavior. One month later, the staff and family complained that she was “underaroused.” On our examination, the patient had severe cogwheel rigidity that had not been diagnosed previously. One hour after administration of benztpine 1 mg, she was “active” again.

Another fear about medication is that it will interfere with a “natural healing process” that occurs after TBI. Evidence obtained from animal models suggests that certain drugs, particularly agents that potently antagonize dopamine type-2 receptors, may interfere with recovery following neuronal injury. Feeney et al. (1982) (135) studied the effect of D-amphetamine on recovery from hemiplegia after ablation of the sensorimotor cortex in rats. They found that D-amphetamine accelerated the rate of recovery, and that this effect was blocked by haloperidol. In addition, haloperidol, when administered alone, resulted in delayed recovery. Importantly, recovery was affected only when the animal was allowed to move during drug administration. This implies that haloperidol delays the recovery process during active rehabilitation, rather than interfering with spontaneous recovery *per se*. In another model, Hovda et al. (1985) (200) found that haloperidol blocked the positive effect of D-amphetamine on recovery of depth perception after visual cortex injury.

It has been suggested that the mechanism of action of haloperidol in delaying recovery also operates through its effects as an  $\alpha$ -adrenergic antagonist (201). Clonidine, an  $\alpha$ 2-adrenergic agonist, and prazosin, an  $\alpha$ 1-adrenergic antagonist, reinstate deficits after sensorimotor cortex ablation (202), an effect not seen with propranolol (203). Other studies have demonstrated that clonidine has deleterious effects on recovery (204, 205). It should be noted that these experimental methods in animals do not produce the same neuropathological findings as contusions

or diffuse axonal injury in humans, and, therefore, may not apply fully to our understanding of the effects  $\alpha$ -adrenergic antagonism following TBI in humans.

In animal studies involving the neurotransmitter  $\gamma$ -aminobutyric acid (GABA), increased GABA function has been associated with greater neuromotor deficits and poorer recovery (206). Increased production of GABA associated with benzodiazepine administration may result in greater glutamate neurotoxicity (207). Diazepam has been found to block recovery of sensory deficits after rat neocortex ablation (208).

The studies cited above relating psychotropic use to impaired neuronal recovery after laboratory-induced brain injury have all used animal models. The study by Rao et al. (1985) (136) appears to offer support for the notion of delayed recovery following administration of haloperidol by virtue of its demonstration of increased duration of posttraumatic amnesia among patients receiving this medication. However, there have been no carefully controlled clinical trials of this important relationship in humans. Interestingly, when the medical records of recovering stroke patients were reviewed, the use of anti-hypertensive medications or haloperidol was associated with poorer recovery (209). Goldstein and Davis (1990) (205) found that when patients who had had ischemic strokes were administered phenytoin, benzodiazepines, dopamine receptor antagonists, clonidine, or prazosin, they showed poorer sensorimotor function and lower activities of daily living than stroke patients who did not receive those drugs.

Many patients are prescribed anticonvulsant drugs (ACDs) after TBI, and may still be receiving them at the time of neuropsychiatric consultation in the period following acute rehabilitation. As noted previously, it is important to ascertain whether such agents were prescribed for the treatment of active seizures, for seizure prophylaxis, or for the treatment of another neuropsychiatric problem. Treatment with anticonvulsant drugs can produce *de novo* cognitive and emotional symptoms (210–212). Phenytoin appears to adversely affect cognition more than carbamazepine (213). Dikmen et al. (1991) (214) described greater cognitive impairment during treatment with phenytoin for prophylaxis of post-traumatic seizures when compared to placebo in a study with 244 patients with TBI. Intellectual deterioration in children on chronic treatment with phenytoin or phenobarbital also has been documented (215). Dikmen et al. (2000) (216) found no adverse cognitive effects of valproate when administered for 12 months after TBI. In a double-blind placebo-controlled study of the cognitive and emotional effects of phenytoin (40 patients) and carbamazepine (42 patients) in TBI patients being treated with these medications for seizure prophylaxis, Smith et al. (1994) (217) noted that both of these medications (but particularly carbamazepine) produced significantly

more cognitive and motor slowing than did placebo. They found that both phenytoin and carbamazepine had negative effects on cognitive performance, especially those that involved motor and speed performance. Although, in the patient group as a whole, the effects were of questionable clinical significance, some patients experienced clinically significant negative cognitive effects during treatment with either of these agents. This is concordant with other observations of carbamazepine's potential to significantly impair cognition in persons with neurological conditions that confer a vulnerability to such effects (218).

However, some patients do tolerate the cognitive effects of valproate and/or carbamazepine relatively well. Minimal impairment in cognition was found with both valproate and carbamazepine in a group of patients with epilepsy (219). Although those included in this study were not TBI patients, this observation suggests that at least some neurologically vulnerable patients may not experience significant cognitive impairment during treatment with these agents. Similarly, Persinger (2000) (220) reported that 12 of 14 patients treated with carbamazepine in the late period following TBI retrospectively reported improvements in episodes of confusion and depression, increases in attention and focus, and reduction or elimination of subtle psychotic-like experiences ("aversive sensed presence"). The author of this study suggests that this finding suggests an electrical (although not epileptic) nature for such symptoms that may be amenable to treatment with carbamazepine or other anticonvulsants.

Among the newer anticonvulsant medications, topiramate, but not gabapentin or lamotrigine, has been demonstrated to adversely affect cognition in healthy young adults (221). Treatment with more than one anticonvulsant (polytherapy) has been associated with increased adverse neuropsychiatric reactions (211). Hoare (1984) (222) found that the use of multiple anticonvulsant drugs to control seizures resulted in an increase in disturbed behavior in children.

Patients who have a seizure immediately after brain injury often are placed on an anticonvulsant drug for seizure prophylaxis. Temkin et al. (1990) (223) showed that the administration of phenytoin acutely after traumatic injury had no prophylactic effect on seizures that occurred subsequent to the first week after injury. Similarly, valproate did not demonstrate any efficacy in preventing late posttraumatic seizures (223). It should be noted that there was a non-significant trend towards a higher mortality during treatment with valproate in this context. Anticonvulsant medications are not recommended after one week of injury for prevention (prophylaxis) of posttraumatic seizures (225). Any patient with TBI who is treated with anticonvulsant medication requires regular reevaluations to substantiate continued clinical necessity for such treatment.

These studies suggest that careful monitoring of cognition, motor function, and other neurobehavioral functions during treatment with any psychotropic compound in persons with TBI is warranted. In general, treatment with these medications should be reserved for patients with neuropsychiatric disturbances that are not fully amenable to treatment through nonpharmacologic means.

## CONCLUSIONS

In this chapter, we have reviewed the role of medication in the treatment of the most frequently occurring neuropsychiatric disturbances that are associated with TBI. Ideally, it would be desirable if the neuropsychiatric problems resulting from TBI could be controlled by nonpharmacologic means alone. However, posttraumatic neuropsychiatric disturbances are associated with significant distress and considerable functional disability, and some of these problems may also endanger the patient and others. In many cases, behavioral treatment and cognitive rehabilitation are of less than optimal benefit in the absence of effective psychopharmacologic treatments of neuropsychiatric disturbances. In other psychiatric conditions such as major depression, there is evidence that delay of effective treatment may result in refractoriness of the condition. For example, Post (1992) (226) reported that recurrent affective disorder becomes more difficult to treat the longer the condition persists. Thus there are theoretical reasons for prompt initiation of pharmacological treatment of neuropsychiatric disturbances in patients with TBI. When appropriately administered, medications may significantly alleviate these problems, improve rehabilitation efforts, and contribute to improved quality of life among persons with TBI.

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# 53

## Pharmacotherapy of Cognitive Impairment

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### INTRODUCTION

Cognitive impairments are among the most common neuropsychiatric sequelae of traumatic brain injury (TBI) at all levels of severity, and typically include impairments of arousal, speed of information processing, attention, memory, language and social communication, and executive functioning (1–5). Although each of these domains of cognitive function may be disrupted by direct injury to cortical, subcortical, or brainstem elements of the distributed cerebral networks that support them, injury to the axons connecting these elements or providing them with the neurochemical input required for their function also contributes to posttraumatic cognitive impairments (6–8). Understanding the neurochemical bases of cognition and the neurochemical consequences of TBI facilitates the development of rational approaches to the pharmacotherapy of posttraumatic cognitive impairments. Although the state of knowledge regarding these issues is at present incomplete, clinicians working with persons with cognitive impairments are well served to stay apprised of this rapidly growing body of information in order to make informed decisions regarding the use of medications in this population.

Toward that end, this chapter provides a review of the pharmacotherapy of cognitive impairment following TBI. To frame that review, definitions of the major domains of cognition most commonly affected by TBI,

their basic neuroanatomy and, where known, their neurochemistry is offered. Next, the neurochemical consequences of TBI particularly relevant to understanding the pharmacotherapy of cognitive and other neuropsychiatric consequences of TBI are reviewed. Thereafter, studies of pharmacotherapies for cognitive impairment following TBI are reviewed and recommendations for the application of those pharmacotherapies are presented.

### COGNITION: DEFINITIONS, NEUROANATOMY, AND NEUROCHEMISTRY

#### Arousal

Arousal is the most fundamental cognitive function, and is supported by a set of selective distributed reticulothalamic, thalamocortical, and reticulocortical networks (9, 10). The principal component of the reticulothalamic portion of the arousal system consists of cholinergic projections arising from the pedunculopontine and laterodorsal tegmental nuclei. These projections terminate in the body of the thalamus as well as the reticular nucleus of the thalamus, the balance of activity between which appears to modulate the degree of thalamic activity. Thalamocortical projections, which are predominantly glutamatergic, activate cortex and prepare it for information processing. The level of cortical arousal, or the readiness of cortex to engage in information processing, is modulated

by the reticulocortical portion of the arousal system. This portion of the arousal system consists of dopaminergic projections arising from the ventral tegmental area of the midbrain, noradrenergic projections arising from the locus ceruleus, serotonergic projections arising from the median and dorsal raphe nuclei, and cholinergic projections arising from the medial septal nucleus and vertical limb of the diagonal band of Broca (to medial temporal structures) and also the nucleus basalis of Meynert (to neocortical, and especially frontal, areas). These projections appear to modulate the activity of widespread areas of neocortex. Collectively, the relative balance between and reciprocal influences of the reticulothalamic and reticulocortical systems determine the individual's clinical level of arousal.

Mechanical injury to any of these elements of the arousal system may impair this most basic cognitive function (6, 8). In more severe injuries, and particularly those in which rotational forces produce shearing or frank hemorrhage in the upper brainstem (i.e., Duret's hemorrhage), arousal may be severely compromised as a result of damage to reticular structures and their reticulothalamic and reticulocortical projections (11). Mechanical injuries of the thalamus, particularly when bilateral, may also compromise cortical arousal and produce persistent vegetative or minimally conscious states (12). Unfortunately, this type of injury is frequently associated with post-TBI fatality (13). Mechanical injury to white matter fibers connecting the several portions of the arousal system (i.e., diffuse axonal injury) produces varying degrees of impaired arousal, decreased speed and efficiency of information processing, and contributes to disturbances in other aspects of cognition (14, 15). Neurochemical perturbations resulting from mechanical injury to these systems, including acute excesses of glutamate, acetylcholine, dopamine, norepinephrine, and serotonin, also contribute to acute disturbances in arousal (16–23). Chronic disturbances in arousal may be due in part to injury-induced deficits in one or more of these neurotransmitters. The role of acute and chronic neurotransmitter dysfunction in disturbances of posttraumatic arousal and other cognitive impairments is discussed in more detail in the next section of this chapter.

### Attention

Sensory gating, selective attention, and sustained attention (vigilance or concentration) are relatively basic cognitive functions. Sensory gating is a pre-attentive process that permits filtering of incoming stimuli in order to admit only a limited amount of information into attentional processing networks (7, 24–26). Selective attention refers to the direction of attentional resources to a stimulus, sustained attention refers to the maintenance of attentional processing on a stimulus, and working

memory denotes the ability to maintain attention to that stimulus in the period immediately following its absence (27).

The boundaries of attentional processes overlap with those of many other cognitive processes, including arousal, perception, recognition, memory, and executive function. Accordingly, attentional disturbances may exacerbate impairments in these other domains of cognition. For example, impairments of attention may interfere with encoding of information (new learning), and thereby produce or exacerbate memory impairments. Similarly, higher-level attentional processes may overlap substantially with executive function, both conceptually and as well as practically given the methods by which executive functions are assessed clinically.

Attentional processes are predicated on several large-scale, selective, distributed neural networks (28; see Mesulam 2000 (9) for a detailed review). These networks include those involved in arousal described above, since arousal is a prerequisite for even the most basic aspects of attention. Additionally, primary and secondary sensory cortices, heteromodal parietal cortical areas, medial temporal (i.e., hippocampal and entorhinal) areas, the striatum and pallidum, several prefrontal (i.e., cingulate, inferolateral, and dorsolateral) cortices, and the axonal connections between them are components of these distributed attentional networks (29–31).

Electrophysiological studies suggest that the neurobiological bases of sensory gating, selective attention, and sustained attention are different (26, 32). Sensory gating appears most strongly related to the function of a cholinergically-dependent hippocampal inhibitory circuit, and is a pre-requisite for the development of selective attention within sensory cortical-hippocampal-frontal networks. Sustained attention is most strongly related to the function of inferior frontal-subcortical and dorsolateral prefrontal-subcortical circuits. The function of these circuits is dependent on a complex set of interactions between the major neurotransmitter systems, including those regulating the availability and function of cortical dopamine, norepinephrine, serotonin, acetylcholine, glutamate, and gamma-aminobutyric acid.

Spatial attention and visuospatial function appear to be served by a network that includes elements of the reticular system, thalamus, superior colliculus, striatum, posterior parietal cortex, frontal eye fields, and parietal cortex (9). As with other attentional processes, most of the major neurotransmitter systems are involved in spatial attention and visuospatial function. Unlike other attentional processes, spatial attention and visuospatial function display a pattern of marked right hemispheric specialization (33, 34). Disruptions in the structure and/or functioning of these networks produce a range of clinical symptoms, although the classic attentional disturbances arising from these right hemisphere attentional

networks include acute confusional states (delirium) and left hemi-inattention (neglect).

As with arousal, acute and chronic neurochemical dysfunction within the networks serving these attentional functions most likely contributes to posttraumatic attentional impairments (24, 35, 36). Impairments in attention may also contribute to problems with the speed of information processing, although the latter is a complex cognitive process predicated not only on attention but also the efficiency and connectivity of the various networks involved in attentional processing and the executive control of attention.

### Memory

Memory is a multifaceted cognitive function that includes both new learning (encoding) and recall (retrieval) of both declarative and non-declarative (implicit and/or procedural) information (37–39). Declarative memory refers to encoding and retrieval of both semantic (or fact) and episodic (or event) information; in other words, declarative memory serves learning and recall of information regarding “who,” “what,” “when,” and “where.” The process of declarative learning, whether verbal or non-verbal, is a hippocampally-dependent process (40, 41). Highly processed multimodal sensory information is transmitted from the inferior parietal (heteromodal) association cortices to the entorhinal-hippocampal complex. When that information produces a sufficiently robust signal in the hippocampus (a process that is, at least in part, predicated on assignment of motivational, emotional, or other “survival-related” significance by amygdala-hippocampal interactions), the process of long-term potentiation is initiated and that information is encoded for later recall. After declarative information is consolidated by this hippocampally-dependent process, retrieving declarative information requires frontal structures to activate the selective distributed networks in which that information was originally encoded. Declarative memory is also therefore highly associative, meaning that memories may be retrieved by reactivation of nearly any part of the network involved in the original encoding of that information or by activation of other networks whose constituent elements are shared by the network involved in the original encoding of that information.

Declarative memory disturbances are relatively frequent consequences of TBI, and may result from injury to the cortical, subcortical, and white matter elements of the networks that serve the various aspects of memory. From a neurochemical perspective, acute excesses of glutamate produce a series of excitotoxic events (i.e., increases in intracellular calcium and activation of second messenger systems) that damage entorhinal and hippocampal areas involved in the development of memory. Damage to these areas results in chronic impairments declarative

memory (42–46). Persistent neurochemical dysfunction in these and other structures required for declarative memory, including alterations in glutamatergic function (43–46) and cholinergic function (7, 24, 47–50), may contribute to posttraumatic impairments in new learning. Injury to the frontal-subcortical elements of this system appears to result in difficulties with efficient retrieval of previously learned information. Information retrieval may be affected by structural and/or neurochemical damage to the frontal-subcortical circuits that subserve this function. In particular, deficits in the availability of dopamine, norepinephrine, and acetylcholine to these circuits appear to contribute to impairments in memory retrieval (51–54).

Procedural memory involves the learning of information of non-declarative nature, and for our purposes is best understood as memory for “how” to perform certain tasks. Procedural memory is predicated on the development and fine-tuning of the sensorimotor-subcortical-cerebellar networks that required for learning and efficiently retrieving complex sensorimotor programs. As such, procedural memory is not hippocampally-dependent and its function and dysfunction are dissociable from declarative memory. Additionally, procedural memory is not associative, but is instead dedicated: it is inflexibly limited to the context (i.e., the specific sensorimotor processes) involved in procedural learning.

Ward et al. (2002) (55) note that procedural memory appears to be less affected by traumatic brain injury than is declarative memory. Recognition of the dissociation between posttraumatic procedural and declarative memory deficits may be relevant to the design of rehabilitation strategies to improve functional memory performance in this population (56). Although procedural memory may be distinguished from declarative memory on anatomical grounds, normal performance in this cognitive domain is dependent on many of the same neurotransmitters required by the frontal-subcortical circuits involved in retrieval of declarative information (57).

### Language

Language refers to the symbolic (both verbal and written) means of communicating thought, and is generally a function of the dominant cerebral hemisphere. The principal domains of language include fluency, comprehension, repetition, and naming, each of which is associated with a selective distributed network specialized to serving its respective language domains (see Damasio and Damasio (2000) (58) for review). Fluency is predicated on a network of frontal structures involving at least dorsolateral, prefrontal motor association, and anterior insular cortices, white matter and subcortical structures through which these areas are connected, and the frontal opercular (Broca’s) area. Output from this network of structures

requires that primary motor cortex and the physical structures needed to communicate verbally or by writing are intact, although communication impairments related to disturbances in elementary motor function are generally distinguishable from true language disturbances (aphasias).

Comprehension of language is predicated on a network of temporoparietal structures, including at least the superior temporal language association cortex (Wernicke's area), inferior parietal heteromodal association cortex, and the white matter structures connecting them. Input to these areas requires that the sensory structures, their connections to primary sensory cortices, and the connection of these areas to sensory association systems are intact. Communication disturbances due to impairments in sensory structures and primary sensory cortices are also generally distinguishable from true language impairments.

The neural networks serving fluency and comprehension are distinct and dissociable, resulting in the production of aphasias referable to dysfunction in their respective networks. Disturbances in the networks subserving fluency produce the "anterior" aphasias, including Broca's and transcortical motor aphasias. The hallmark feature of these aphasias is impaired language syntax (i.e., agrammatisms), reduced phrase length, and undue word finding pauses. Disturbances in the networks subserving comprehension produce the "posterior" aphasias, including Wernicke's and transcortical sensory aphasias. The hallmark feature of these aphasias is impaired language semantics, including impaired understanding of word or phrase meaning and ineffective monitoring of language output (e.g., substitutions, phonemic paraphasias, neologisms, etc.).

Repetition is served by a distinct network comprised of Wernicke's area, a phonological output area at the anterior border of Wernicke's area, Broca's area, and the arcuate fasciculus which connects the posterior and anterior language areas. Disruption of any of these areas produces deficits in repetition. Disruption of the phonological output area or arcuate fasciculus may produce an isolated disruption of repetition, a problem referred to clinically as conduction aphasia. The neural networks subserving naming are widely distributed, and overlap substantially with those upon which fluency, comprehension, and repetition are predicated. Consequently, impairments of naming are commonly associated with any disruption sufficient to produce impairments in these other areas of language.

Disturbances of language and functional communication are not uncommon among persons with TBI (59–64), and may negatively affect functional outcome after TBI (65). Frank aphasias are generally associated with direct injury to cortical language areas or their subcortical white matter connections, and are relatively less common after TBI than are more subtle functional

communication impairments. These subtle language disturbances, such as mild word-finding and naming problems, are common consequences of TBI across the spectrum of injury severity, and tend to be more strongly associated with anterior (i.e., frontal and temporopolar) rather than posterior (temporoparietal) lesions (63).

The neurochemistry of posttraumatic language impairments is less clearly understood than is the neurochemistry of posttraumatic impairments of arousal, attention, and memory. Several reports of the pharmacotherapy of aphasia suggest a role for augmentation of dopamine (66–72) and acetylcholine (73) in the treatment of language disturbances in persons with stroke and TBI, although findings from such studies are not universally positive (74). While inferential reasoning of the neurochemistry of language from pharmacotherapeutic interventions should be undertaken with caution, these reports suggest that dopaminergic and/or cholinergic systems may be reasonable targets for the treatment of posttraumatic language disturbances.

### Prosody

Prosody refers to the affective import and kinesics of language (75, 76). Disturbances of prosody, or the aprosodias, demonstrate a pattern of non-dominant hemispheric specialization. The nondominant hemisphere structures and networks serving prosody are simplistically understood as homologous with those in the dominant hemisphere serving the syntax and semantics of language. Impaired function of the nondominant frontal structures involved in language may produce disturbances in the affective and kinesic aspects of language production, resulting in flat or monotonous expression that fails to communicate effectively the emotional relevance and subtlety of the information expressed. Impaired function of the non-dominant temporoparietal structures involved in language may produce disturbances in the appreciation of the affective and kinesic aspects of the communications of others.

At present, little is known about the frequency of either the posttraumatic aprosodias or their neurochemistry. It has been suggested that dopaminergic dysfunction may influence prosody (77). However, Raymer et al. (2001) (66) observed no improvements in prosody despite improvements in fluent language in a patient with a post-stroke aphasia treated with bromocriptine. Although the neurochemistry and pharmacotherapy of the aprosodias is poorly understood, clinicians should be mindful of such language disturbances as they may mask affective or mood disturbances experienced by persons with TBI and may impair the ability of these individuals to engage in effective social communication despite otherwise intact language.

## Praxis

Praxis refers to the on-demand integration of task understanding and execution, and impairments of this ability are referred to as apraxias (78, 79). Ideomotor apraxia denotes a condition in which an individual is unable to perform on demand a relatively simple (ostensibly “single-step”) task such as brushing one’s hair or teeth, pointing to objects, or pantomiming simple actions. Ideational apraxia denotes a condition in which the sequential linking of several ideomotor tasks is impaired.

Praxis displays a pattern of dominant hemisphere specialization, and the neural networks subserving this domain of cognition appear to overlap substantially with those serving language (10, 80). Consequently, the apraxias tend to be associated with the aphasias, and particularly with the nonfluent aphasias. The neurochemistry of praxis is not well understood, although it has been suggested that striatal dopamine deficits may contribute to the development of apraxia (81). As such, interventions targeting the aphasias, when effective, may be expected to improve concurrent disturbances of praxis. However, Raymer et al. (2001) (66) observed no improvement in limb apraxia despite improvement in nonfluent aphasia in a patient with post-stroke aphasia treated with bromocriptine. The specific neurochemistry of apraxia therefore remains uncertain, as does the neurochemical basis for pharmacotherapy of posttraumatic impairments in praxis.

## Complex Cognition

Complex cognitive functions, including comportment (“social intelligence”), motivation, and executive function are also frequently impaired after TBI (82–86). Comportment describes the manner in which one interacts with others, and involves the integration of emotional (i.e., limbic and paralimbic) information with an understanding of the rules of social interaction. As such, we have described this function as the foundation of “social intelligence” (87). This term refers to the ability to understand and integrate self-assessment with social cueing, and deficits in social intelligence may result in socially inappropriate and maladaptive behavior. This cognitive function is most often ascribed to the lateral orbitofrontal-subcortical circuit (88), given the role of this cortical area in the integration of limbic-paralimbic information with other socially or environmentally relevant information.

Motivation refers to the process of generating, directing, and sustaining goal-directed cognition, emotion, and behavior. Dysfunction of this process results in apathy: a reduction in goal-directed motor, emotional, and cognitive activity (89). Motivation is most often ascribed to the anterior cingulate-subcortical circuit (88–90).

Although the occurrence and treatment of both comportmental and motivational impairments overlap substantially with those of impaired cognition, these impairments typically are more commonly regarded as behavioral rather than cognitive disturbances *per se*. As such, treatment of these problems is discussed in the chapter describing pharmacotherapies of neuropsychiatric disturbances elsewhere in this volume.

Executive function refers to a collection of abilities including: categorization and abstraction; systematic memory searching and information retrieval; problem solving; self-direction; planning and organization of cognition and behavior; independence from external environmental contingencies; maintenance of and fluent shifting between information or behavior sets; and use of language to guide behavior. These are the functions that are most immediately regarded as “intelligence” by patients, their families, and their care providers.

Executive function is most often ascribed to the dorsolateral prefrontal-subcortical circuit, and in particular its ability to integrate the processing and interaction of more “basic” cognitive processes carried on elsewhere in the brain. Executive dysfunction is a relatively common consequence of TBI, and may arise as a direct effect of injury to the dorsolateral prefrontal cortex, the subcortical elements connect to this cortical area, or the axonal connections between them (82). The function of the dorsolateral prefrontal-subcortical circuit serving executive function is dependent on a host of neurotransmitters including glutamate (serving as the primary excitatory neurotransmitter), acetylcholine, dopamine, norepinephrine, serotonin, (serving various modulatory functions), and gamma-aminobutyric acid (GABA, serving as the primary inhibitory neurotransmitter), among others (87, 88, 91). Consequently, posttraumatic disturbances in the function of any of these neurotransmitters may contribute to executive function impairments. By extension, pharmacotherapies that improve the function of posttraumatic impairments in these neurotransmitter systems would be expected to produce improvements in executive function.

## Summary of the Neuroanatomic and Neurochemical Bases of Cognition

In this section we reviewed the basic neuroanatomy and neurochemistry of several cognitive domains in which posttraumatic impairments are common. Although normal cognition ultimately depends on a complex set of neurotransmitter, neuroactive peptides, neurohormones, second messenger system, and genetically-regulated neurochemical processes and interactions, several simple themes relevant to currently available pharmacotherapies are apparent. Glutamate-mediated neuronal damage and/or long-term glutamatergic dysfunction (either excess or deficit) may adversely affect a host of cognitive functions,



including arousal, attention, memory, and executive function. Catecholamine (i.e., dopamine and norepinephrine) dysfunction appears particularly important to cortical aspects of arousal attention, speed of processing, language, executive function, and perhaps also memory retrieval. The role of serotonin in cognition is uncertain; augmentation of serotonin via nonselective serotonin reuptake inhibitors does not appear to be of direct benefit to cognition, but may indirectly affect cognition via improvement of comorbid disorders such as depression (92). Whether more limited alteration of serotonergic activity (e.g., alteration of action at 5HT-3 receptors) improves cognition directly or indirectly through modulation of other neurotransmitter systems is a matter of present investigation (see Buhot et al. 2000 (93) for review). Cholinergic function appears important to both subcortical and cortical aspects of arousal, attention, and memory, and may also play an important role in language and executive function. In the next section of this chapter, we will review the evidence for neurotransmitter dysfunction following TBI in order to frame the neurochemical basis of pharmacotherapies for posttraumatic cognitive impairments.

### THE NEUROBIOLOGICAL BASES OF COGNITIVE IMPAIRMENT FOLLOWING TBI

Cognitive deficits arising from penetrating and/or focal trauma are often understandable given the functions known to be subserved by the site of injury; for example, executive impairments following severe bifrontal contusion and/or white matter injury, impaired anterograde memory following bilateral entorhinal-hippocampal injury, and so on (94). However, the etiology of cognitive impairments following non-penetrating (or “non-focal”) injuries is relatively less well understood. Cytotoxic processes such as calcium and magnesium dysregulation, free radical injury, neurotransmitter (especially glutamate and cholinergic) excitotoxicity, and diffuse axonal injury due to straining and shearing biomechanical forces result from non-penetrating, non-contusional injuries (see McIntosh et al. (1999) (95) and Halliday (1999) (96) for review). These processes functionally and structurally disrupt the neural networks subserving neuropsychiatric function (i.e., cognition, emotion, and behavior). Studies of neurochemical changes subsequent to TBI suggest that alterations in neurotransmitter production and/or delivery occur within these networks both acutely and chronically, and therefore play a role in the development of cognitive impairments following TBI. As discussed in the following sections of this chapter, all of the major neurotransmitter systems, including glutamate, dopamine, norepinephrine, serotonin, and acetylcholine, are elevated in the acute period following TBI, a process that we

suggest may be simplistically understood as an acute traumatically-induced “neurotransmitter storm.” However, the timing and/or eventual recollection of these neurotransmitter elevations influences the relevance of each of these systems to acute and/or chronic posttraumatic cognitive impairments.

### Glutamate

TBI-induced glutamatergic disturbances are almost certainly important in the genesis of injury to areas critical to neuropsychiatric function (see Obrenovitch and Urenjak (1997) (19) for a detailed review). Excessive release of the amino acid neurotransmitters glutamate and aspartate appears to be at least in part responsible for traumatically-induced neuronal injury, particularly to areas in which these neurotransmitters play key roles (i.e., hippocampus and frontal cortices) (97–99). The degree of elevation of these excitatory amino acid neurotransmitters appears to be associated with the severity of injury and post-injury survival (100–102). The principal neurotoxic effects of glutamate are generally attributed to its action at N-methyl-D-aspartate (NMDA) receptors. When glutamate activates an NMDA receptor, it opens a channel in the cell membrane that permits influx of calcium. When excessive amounts of calcium enter the cell, oxidative processes and activation of proteolytic enzymes ensue, and the axonal terminus of the neuron is injured or destroyed. Even where such excesses are not directly excitotoxic, they tend to “drive” glucose utilization, which may exceed the capacity of the brain for oxidative metabolism, thereby producing toxic accumulations of lactate (103).

Cerebral glutamate levels are elevated within hours following TBI and appear to remain elevated for at least the first week following TBI in humans (104–107). The rate of return to normal levels of glutamate may be adversely affected by concurrent hypoxia (108). With or without such complicating factors, the rate at which glutamate levels return to pre-injury baseline – if they do indeed completely normalize after TBI – is uncertain. The rate of decline of glutamate levels observed in studies performed to-date suggests a trend towards normalization of cerebral glutamate in the weeks following TBI. However, early elevations of glutamate may permanently damage cortical areas (109) and thereby contribute to persistent posttraumatic cognitive impairments.

Animal models suggest that antagonism of glutamate receptors may attenuate the severity of neuronal injury following either focal ischemia (110) or trauma (98, 99). Additionally, glutamate-mediated excitotoxicity may be attenuated by therapeutically induced, but not spontaneous, cerebral hypothermia delivered in the acute post-injury period (111). Unfortunately, there are at present no widely available pharmacotherapies that effectively

limit the destructive effects of acute excesses of glutamate or that ameliorate cognitive or other neuropsychiatric problems predicated on glutamate-induced neuronal damage (112).

Memantine and amantadine, two moderate-affinity uncompetitive NMDA receptor antagonists, are of theoretical interest to both the prevention of glutamate-mediated neurotoxicity in TBI and also the remediation of posttraumatic cognitive impairments predicated on glutamatergic dysfunction. Although there is evidence that memantine confers neuroprotection from glutamate-mediated excitotoxicity when administered shortly after experimental TBI in animals (113), there are at present no studies demonstrating neuroprotection from either amantadine or memantine in human TBI. Memantine and amantadine appear to indirectly increase striatal, prefrontal cortical, and nucleus accumbens dopamine function through their actions at glutamate receptors on midbrain dopaminergic neurons (114–117) or other yet undetermined mechanisms (118). The effects of these medications on both glutamate function and dopaminergic function may account for the purported benefit of memantine among persons with cognitive impairments due to Alzheimer's disease (119–122), cerebrovascular disease (120–123), and Wernicke-Korsakoff syndrome (124). As discussed in the next section, amantadine has been observed to improve arousal, attention, motivation, and other frontally-mediated functions in persons with TBI (125–129). Although encouraging of the potential application of this medication and other uncompetitive NMDA receptor antagonists to the treatment of posttraumatic cognitive impairments, the role of the glutamatergic properties of these agents towards that end is at present uncertain.

### Catecholamines

Discrete lesions to ascending monoaminergic projections may interfere with the cognitive function served by the networks dependent upon them (130). Monoaminergic afferents course from the brain stem anteriorly, curving around the hypothalamus, the basal ganglia, and the frontal cortex, placing them in anatomical areas that are especially vulnerable to strain and shear forces that occur during TBI. Catecholamines alter the signal-to-noise ratio in the circuits that process information (131–133). In the setting of optimal catecholamine levels, the processing of contextually relevant cognitive, emotional, or behavioral information (signal) is enhanced and processing of background information (noise) is inhibited. As such, catecholamines serve as key modulators of information processing circuits in the brain. Because dopamine and norepinephrine exhibit an inverted U-shaped dose-response curve with respect to their effects on cortical information processing (9), either deficient or excessive dopamine may interfere with this process.

Two studies found markedly elevated plasma catecholamine levels after acute head injury in humans (22, 134). Acute elevations of these neurotransmitters are predictive of poor recovery from TBI (17, 22, 23). Whether such elevations are themselves sufficiently injurious to contribute to poor recovery after TBI or are instead simply a proxy for injury severity is not clear.

Also unclear is the role of catecholaminergic dysfunction in the development of persistent posttraumatic cognitive impairments. Tang et al. (1997) (18) suggested that striatal hyperdopaminergia contributes to post-TBI memory deficits in recently injured animals, antagonism of which improved visual memory performance. This finding appears to contradict the inference of reduced dopamine function drawn from observations of cognitive benefits following augmentation of dopaminergic function (using methylphenidate, for example) among persons with TBI in the days to weeks following injury (135, 136) and the observation that robust dopamine antagonism delays recovery from posttraumatic amnesia (137). However, it is consistent with the suggestion that either hyper- or hypodopaminergia may interfere with cognition following TBI. Very few other experimental-injury studies (20, 138) offer support for the hypothesis that cerebral catecholamine levels are chronically altered by TBI, and only one human study offers indirect evidence of relationship markers of dopaminergic or noradrenergic function and long-term cognitive deficits in traumatically brain-injured humans. Konrad et al. (2003) (35) studied 26 children with TBI, 31 children with attention deficit hyperactivity disorder (ADHD), and 26 healthy comparison children. Subjects with TBI and ADHD excreted significantly more urinary normetanephrine in resting situations and less urinary epinephrine after cognitive stress, and showed a decreased blink rate (an indirect measure of dopamine function) compared to normal controls. Children with TBI also demonstrated a higher excretion of metanephrine in the resting situation in comparison to children with ADHD and controls. Children with ADHD showed a higher tonic activity of the noradrenergic system and a less adaptive epinephrine excretion in response to cognitive stress, and children with TBI were impaired in their tonic epinephrine excretion. These observations suggest the possibility of long-term alterations in systemic monoaminergic function following TBI, but they offer only indirect evidence of posttraumatic dysfunction in cerebral monoaminergic systems.

Although evidence of direct, persistent, and statistically significant injury to catecholaminergic afferents following TBI is at present lacking (139), genetically-determined individual differences in the metabolism of these neurotransmitters by catechol-O-methyltransferase (COMT) may contribute to posttraumatic cognitive impairments. Substitutions in the gene sequence for COMT at codon 158 (Val/Met) result in expression of

an enzyme with either high activity (COMT-val) or low activity (COMT-met) (140). Persons homozygous for the COMT-val isoform appear to metabolize catecholamines more efficiently than persons homozygous for the COMT-met isoform, and heterozygotes (i.e., COMT-val/met) metabolize catecholamines with an intermediate level of efficiency. In a study of 123 persons with TBI and posttraumatic executive dysfunction, Lipsky et al. (2002) (141) observed the highest levels of executive dysfunction on the Wisconsin Card Sorting Task (generally regarded as a measure of executive function) among subjects homozygous for the fast-acting COMT enzyme, intermediate levels of impairment among heterozygotes, and the lowest levels of impairment among subjects homozygous for the slow-acting COMT enzyme. This finding suggests that even if TBI produces only modest injury to reticulocortical catecholaminergic projections, individual differences in the metabolism of these neurotransmitters might in some persons (i.e., those with the fast-acting COMT enzyme) transform modest structural injury into substantial functional impairments in catecholamine-dependent cognitive functions.

In summary, while the extent of dopaminergic and noradrenergic dysfunction in the late period following TBI remains uncertain, pre-injury genetic differences in the metabolism of these neurotransmitters may contribute to posttraumatic cognitive impairments. The implications of such finding with respect to long-term neuropsychiatric disturbances require further study.

### Serotonin

Serotonergic projections to frontal cortical areas are susceptible to biomechanical injury, and both diffuse axonal injury and contusions may produce dysfunction in this neurotransmitter system. Secondary neurotoxicity that is caused by excitotoxins and lipid peroxidation may also damage serotonergic projections (142). Pappius (1989) (21) demonstrated widespread increases in hemispheric serotonin levels following experimentally induced brain injury in rats, and noted that increases in serotonin appeared to produce decreases in cerebral glucose utilization. Busto et al. (1997) (143) observed a prompt increase in the extracellular levels of serotonin in cortical regions adjacent to the impact site in an experimental injury study in rats. Tsuiki et al. (1995) (144) demonstrated in an experimental injury paradigm that serotonin synthesis was significantly increased in cortical areas throughout the injured hemisphere, particularly in the dorsal hippocampus and hippocampal area CA3, in the medial geniculate nucleus, and in the dorsal raphe nucleus. These authors observed depression in cortical glucose use in areas with increased serotonin synthesis. Eghwurdjakpor et al. (1997) (20) demonstrated a rapid increase in hemispheric concentrations of serotonin,

dopamine, and norepinephrine shortly after trauma experimentally induced traumatic brain injury in rats, with continued increases to three to four times control levels by 24 to 48 hours postinjury. These authors also report significant regional differences in serotonin levels after experimental TBI, with increases in the cerebral hemispheres but decreases in the spinal cord.

Findings regarding posttraumatic cerebral serotonin levels are discrepant, but such discrepancies may be attributable to between-study differences in the sites from which CSF samples are obtained. For example, Vecht et al. (1975) (145) and Bareggi et al. (1975) (146) found that lumbar cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) was below normal in conscious patients and normal in patients who were unconscious. Decreased CSF levels of serotonin are reported by Karakucuk et al. (1997) (142) in 45 adults undergoing minor surgery with spinal anesthesia within 24 hours of TBI. However, Porta et al. (1975) (147) demonstrated elevated ventricular CSF 5-HIAA levels in patients within days of severe TBI. These findings suggest that ventricular sampling in humans may more accurately reflect alterations in cerebral serotonin levels after TBI than lumbar cerebrospinal fluid sampling. Additionally, focal and diffuse lesions may result in differences with respect to monoaminergic alterations after TBI. For example, Van Woerkom et al. (1977) (148) investigated patients with frontotemporal contusions and those with diffuse contusions. They documented decreased levels of 5-HIAA in patients with frontotemporal contusions, but increased 5-HIAA levels in those with more diffuse contusions.

The evidence in both animal and human studies suggests that TBI results in acute increases in hemispheric serotonin levels and also that such increases are associated with decreased cerebral glucose utilization. As a result of decreasing cortical metabolism, acute elevations of serotonin may in part contribute to posttraumatic cognitive impairments during the acute injury period. It stands to reason that augmentation of serotonergic function in the acute injury period would be of little benefit cognitively. Consistent with that reasoning, Meythaler et al. (2001) (149), in a placebo-controlled trial of sertraline for arousal and attentional impairments in 11 subjects with severe TBI in the acute rehabilitation setting, failed to find a statistically significant treatment effect on these cognitive functions. Although their small sample size precludes generalization of their findings, they suggest that augmentation of serotonergic function alone is insufficient to produce marked improvements in cognition among persons with recent severe TBI. Similarly, Wilson and Hamm (2002) (150) observed no improvement in memory function in experimentally-injured rats treated with fluoxetine. These findings suggest that selective serotonin reuptake inhibitors (SSRIs) such as these should not at the present time be regarded as agents with direct

cognitive-enhancing properties in the setting of acute severe TBI.

Whether the SSRIs are without such effects in the late period follow TBI is uncertain. Schmitt et al. (2001) (151) investigated the cognitive effects of several SSRIs and demonstrated significant improvements in verbal fluency among healthy middle-aged adults treated with sertraline 50–100 mg when compared to treatment with placebo. The authors of this study attributed that effect to sertraline's modest ability to inhibit dopamine reuptake. Fann et al. (2001) (92) describe improvements in psychomotor speed, recent verbal memory, recent visual memory, general cognitive efficiency, and patient-reported perception of cognitive symptoms during treatment of post-TBI depression with sertraline. It is possible that treatment with sertraline may confer cognitive benefits on the basis of resolving depression alone, as a function of augmenting either frontal serotonergic or dopaminergic function, or by both these and other mechanisms.

Similarly, Horsfield et al. (2002) (152) performed an eight-month open-label study of the effects of fluoxetine 20–60 mg/day in five patients with TBI and varying levels of depression in order to determine whether this medication conferred mood and/or cognitive benefits. They observed improvements in mood among persons with such symptoms, and demonstrated improvement on several measures of attention, processing speed, and working memory in this small group of patients. Their findings are consistent with the observations of Fann et al. (2001) (92) with respect to improved cognition in association with reduced depressive symptoms, but extend that finding to suggest a possible benefit of this serotonergic augmentation on cognition more generally. The authors of this study also note fluoxetine's ability to stimulate expression of brain-derived neurotrophic factor and its specific tyrosine kinase receptor. Such effects have been demonstrated to produce neuritic elongation and increased dendritic branching density of some hippocampal neurons in rodents. Although it is possible that similar mechanisms may be operative in humans, the sample size and findings of the Horsfield et al. (2002) (152) study do not support this interpretation at present. Instead, interpreting their findings as reflecting the activating effects of fluoxetine (which may operate through a variety of neurochemical mechanisms) is both simpler and more likely to be correct.

At present, it appears that serotonergic augmentation using SSRIs may be of benefit in the treatment of depression following TBI, and that alleviation of depression is associated with improvement in cognition. It is not clear that these agents, which are non-selective with respect to their effects at a receptor level, confer any direct benefit on cognition alone. Receptor-specific modulation of serotonergic function (i.e., agonism of 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub> or 5-HT<sub>4</sub> receptor, or antagonism of 5-HT<sub>1A</sub> or 5-HT<sub>3</sub>

and 5-HT<sub>1B</sub> receptors) may afford cognitive benefits (93). Consistent with that suggestion, Kline et al. (2001) (153) demonstrated improvement in spatial memory in experimentally-injured rats treated with the 5HT<sub>1A</sub> receptor antagonist repinotan. Additional studies are needed to clarify the cognitive effects of agents that modify receptor specific serotonergic activity among persons with TBI.

### Acetylcholine

Findings from both basic and clinical studies suggest that TBI produces acute elevations and long-term deficits in cortical cholinergic function. Multiple studies (48, 154–160) demonstrate this pattern of cholinergic dysfunction following experimentally-induced TBI in rodents, as well as a robust relationship between chronic post-traumatic cholinergic deficits and spatial memory impairments. One of the most compelling demonstrations of relatively selective cholinergic injury following TBI is the report of Schmidt and Grady (1995) (139). They induced a fluid-percussion head injury sufficient to cause a 13- to 14-minute loss of righting reflex in rats anesthetized with halothane. Rats with experimentally induced midline injury suffered significant bilateral reductions in cholinergic neurons, including reductions in area Ch1 (medial septal nucleus; 36%), Ch2 (nucleus of the diagonal band of Broca; 44%), and Ch4 (nucleus basalis of Meynert; 41%). Among animals with lateralized injuries, similarly severe losses of cholinergic neurons were observed ipsilateral to the injury site and lesser but nontrivial (11–28%) losses were observed contralaterally. The authors note that these losses did not extend to brainstem cholinergic nuclei (Ch5 and Ch6), and there were no observable effects on forebrain dopaminergic or noradrenergic innervation. These findings suggest that cholinergic deficits may be the most prominent type of chronic posttraumatic neurotransmitter disturbance.

TBI in humans produces the same pattern of cholinergic dysfunction as is reported in the experimental injury literature, with acute elevations of cerebral acetylcholine followed by chronic cholinergic deficits. Grossman et al. (1975) (161) demonstrated that patients with TBI had elevated acetylcholine levels in fluid obtained from either intraventricular catheters or lumbar puncture in the acute period following TBI. Dewar and Graham (1996) (162), Murdoch et al. (16, 163) demonstrated loss of cortical cholinergic afferents with concurrent preservation of post-synaptic muscarinic and nicotinic receptors several weeks after severe and fatal TBI. Arciniegas et al. (7, 25, 26), using the hippocampally-mediated cholinergically-dependent P50 evoked waveform response to paired auditory stimuli as a marker of cholinergic function, demonstrated electrophysiologic abnormalities in patients with chronic symptoms of impaired auditory gating,

attention, and memory in the late (>1 year) period following TBI. In a subsequent study, Arciniegas et al. (2003) (24) demonstrated that this electrophysiologic abnormality is present in the majority of persons with persistent attention and memory complaints in the late period following TBI. Collectively, these findings support the hypothesis that cholinergic function is chronically deficient among many persons with TBI and that cholinergic deficit may be a significant contributor to posttraumatic cognitive impairments.

Given the role of acetylcholine in arousal and attention (9, 10), memory (164, 165), and executive function (166), and the evidence suggesting that cholinergic deficits contribute to posttraumatic cognitive impairments, pharmacotherapies that augment cholinergic function may improve posttraumatic cognitive impairments. These therapies are discussed in more detail in the next section of this chapter.

### Summary of Post-Traumatic Neurochemical Disturbances

Animal and human studies suggest that most of the major neurotransmitter systems are acutely activated by mechanical brain injury. These excesses appear to result in a complex set of cerebral, and hence cognitive, dysfunctions. Neurotransmitter disturbances appear to be not only consequences of TBI but also contributors to brain injury. Excesses of glutamate are excitotoxic and may permanently damage areas with dense glutamatergic innervation, including frontal, striatal, and medial temporal (i.e., hippocampal) areas. There is, at present, no evidence to support chronic reductions in glutamatergic function after TBI. However, it is conceivable that improving the efficiency of glutamatergic neurotransmission with agents like memantine, amantadine, or neramexaane (another uncompetitive NMDA receptor antagonist presently under study in humans) may improve cognitive and other neurobehavioral functions in persons with TBI.

Acute catecholaminergic excesses after TBI appear predict poor outcome following TBI; when present, such increases may simply be a marker of injury severity in the studies in which they were assessed. Although evidence of chronic reductions in catecholaminergic function after TBI and/or a relationship of such to posttraumatic cognitive impairments in humans is lacking, more modest reductions in these neurotransmitters may in some genetically vulnerable persons (i.e., those with a fast-acting COMT enzyme) contribute to posttraumatic impairments in catecholamine-dependent cognitive functions. Alternatively, persons with traumatic lesions to catecholamine projections would be expected to develop cognitive impairments in the areas to which the lesioned fibers project. The cognitive functions served by the cerebral

(i.e., frontal) areas to which these catecholaminergic fibers project are at greatest risk for disruption, including arousal, attention, speed and efficiency of information processing, executive function, and perhaps also language.

At present, there is also a dearth of evidence to support a relationship between posttraumatic dysfunction in serotonergic systems and cognitive impairment. Acute serotonergic excesses are associated with decreased cortical metabolism in the areas in which such excesses occur. In the acute post-injury period, serotonin-induced cerebral hypometabolism may contribute to cognitive dysfunction. It is not clear whether such excesses normalize, persist, or transition to posttraumatic deficits in serotonergic function. There is some evidence that treatment with the sertraline (92) or fluoxetine (152) may facilitate cognitive improvements in persons with depression following TBI. However, it does not appear that these agents facilitate cognitive improvements alone, at least not among persons with severe TBI (149). Consequently, the contribution of serotonergic dysfunction to posttraumatic cognitive impairments in the absence of comorbid posttraumatic depression is uncertain.

There is considerable animal and human evidence of acute posttraumatic excesses of acetylcholine and chronic posttraumatic reductions in cholinergic function. Because acetylcholine is a major contributor to the function of brain systems involved in arousal, attention, memory, language, and executive function, cholinergic deficits would be expected to contribute posttraumatic cognitive impairments.

The pharmacotherapy of TBI should be considered in the context of these findings. As will become clear in the next section of this chapter, the pharmacotherapeutic studies performed to-date appear to support most strongly the suggestion that augmentation of catecholaminergic and cholinergic function, and perhaps also glutamatergic function, are useful neurochemical targets for pharmacologic intervention among persons with posttraumatic cognitive impairments.

### PHARMACOTHERAPY OF POST-TRAUMATIC COGNITIVE IMPAIRMENTS

As with any pharmacotherapy for the neuropsychiatric (i.e., cognitive, emotional, or behavioral) sequelae of TBI, the basic principles of pharmacotherapy (see Chapter 52, "Pharmacotherapy of Neuropsychiatric Disturbances") in this population should be followed. For purposes of this discussion, we will assume that prior to initiating any pharmacologic treatment for posttraumatic cognitive impairments the treating clinician has first completed a thorough psychiatric, developmental, and neurological evaluation. When subsequently considering pharmacotherapy of cognition, two issues require additional

attention. First, the presenting cognitive complaints must be carefully assessed, defined, and operationalized, preferably through the use of objective measures of cognition. These measures may include “bedside” tests such as the Mini-Mental State Examination (167), any of several versions of the Clock Drawing Test, the Frontal Assessment Battery (168) or other similar measures of frontally-mediated cognition, but are better assessed through formal neuropsychological testing. Measures that are sensitive to both global cognitive impairment as well as impairments of speed of information processing, attention, memory, language, and executive function should be included in any pre-treatment cognitive assessment.

Second, the use and effectiveness of all ongoing treatments must be reevaluated, including both pharmacologic and non-pharmacologic therapies (whether prescribed and/or self-administered). Several classes of medications are of particular concern. Anticonvulsants such as phenytoin and carbamazepine may exacerbate cognitive impairments among persons with TBI. In a double-blind placebo-controlled study of phenytoin (40 patients) and carbamazepine (42 patients) in TBI patients being treated with these medications for seizure prophylaxis, Smith et al. (1994) (169) report that both of these medications (but particularly carbamazepine) produced significantly more cognitive and motor slowing than did placebo. Dikmen et al. (1991) (170) also observed greater cognitive impairment during treatment with phenytoin for prophylaxis of posttraumatic seizures when compared to placebo in a study with 244 patients with TBI. Additionally, phenytoin conferred no benefit against the development of post-traumatic seizures when used after the first week post-TBI. Both studies suggest that careful monitoring of cognition during treatment with anticonvulsants in brain-injured patients is warranted, and that such treatment should be reserved for patients with clearly established posttraumatic seizure disorders. Typical antipsychotic medications (e.g., haloperidol, fluphenazine, thioridazine, chlorpromazine) may exacerbate cognitive impairments among persons with TBI (171) and may prolong the period of posttraumatic amnesia (137). Benzodiazepines are known to impair memory and other aspects of cognition even among individuals without brain injuries (172), and there is some evidence supporting the common clinical belief that these agents impair cognitive performance among persons with TBI (173). It is concerning that prescription of anticonvulsants, typical antipsychotics, and benzodiazepines remains common in this population. It is sometimes the case that such treatments have not been properly applied, are predicated on misdiagnosis of the problem, or are the result of poor communication among treating professionals regarding the problem in question. When treating posttraumatic cognitive impairments, the most appropriate first pharmacological recommendation is to eliminate

these medications. If after eliminating these medications there remain cognitive, emotional, or behavioral problems that require treatment, nonpharmacologic therapies should be offered. When these interventions fail to afford improvement in posttraumatic cognitive performance, then medications may be required.

As noted in the previous sections of this chapter, advances in our understanding of the neurochemistry of TBI have been used to develop *a priori* hypotheses to guide the selection of pharmacotherapeutic agents in some treatment studies. While these studies are few in number, continued development of the pharmacotherapeutic literature in this area should be predicated on such *a priori* hypothesis rather than on the basis of extrapolation from the treatment of other neuropsychiatric disorders. At present, our understanding of the neurochemical consequences of TBI yields three principal themes in the pharmacotherapy of posttraumatic cognitive impairments: modulation of glutamatergic function, augmentation of catecholaminergic function, and enhancement of cholinergic function.

There are at present no proven therapies with which to limit the effects of glutamate-mediated excitotoxic injury among traumatically brain-injured persons. It is also not clear whether or to what extent acute alterations or long-term dysfunction of glutamate function contribute to posttraumatic cognitive impairments. This is likely to be an area of increasing research in the field of TBI, and clinicians should be aware of the possibility that agents affecting glutamatergic function may find applications in the pharmacotherapy of posttraumatic cognitive impairments. However, given the lack of data regarding this approach we will not consider further this issue.

The majority of the pharmacotherapeutic literature in this field focuses on augmentation of catecholaminergic function, cholinergic function, or both. As discussed above, chronic cholinergic and/or catecholaminergic dysfunction contribute to cognitive impairments following TBI. While the experimental and human literature offers stronger evidence of chronic posttraumatic cholinergic dysfunction, clinical evidence suggests a potentially useful role for augmentation of either or both of these neurotransmitter systems in persons with posttraumatic cognitive impairments. However, the interindividual response to such agents is not uniform (136). Some patients respond to psychostimulants, some to cholinesterase inhibitors, some require medications from both classes, and some respond to neither class of medication. Selecting an appropriate treatment for a given patient might be made easier if clinical markers of dysfunction in these systems were available. However, simple, inexpensive, and widely available markers of *in vivo* neurotransmitter function are at present lacking.

In the absence of widely available markers of neurotransmitter dysfunction, pharmacotherapeutic studies performed to-date generally employ agents observed to

be effective for the treatment of cognitive impairments among persons with phenotypically similar but etiologically distinct neuropsychiatric disorders. For example, the attention deficits of persistently impaired TBI survivors sometimes superficially resemble those of patients with attention-deficit hyperactivity disorder (ADHD). Given this similarity, psychostimulants (e.g., methylphenidate, dextroamphetamine) and dopaminergically active medications (amantadine, bromocriptine, L-dopa/carbidopa, etc.) have been used with some success for the treatment of posttraumatic impairments of arousal, processing speed, attention, and executive function. Because posttraumatic memory disturbances may in some respects resemble those observed among persons with Alzheimer's disease, agents used for the treatment of cognitive impairments in Alzheimer's disease have been studied in persons with similar problems following TBI. Although there are some differences in the relative predominance of encoding and retrieval deficits between these conditions, the cholinesterase inhibitors have been used with some success among patients with posttraumatic memory impairments.

Complicating the matter of selecting the agent most likely to improve posttraumatic cognitive impairment in an individual patient is the relative paucity of rigorously conducted clinical studies upon which to base treatment decisions. Although the pharmacotherapy of posttraumatic cognitive impairments is the most extensively studied area of neuropsychiatric treatment in this population to-date, the limited number and methodological problems of these studies limit their generalizability to everyday clinical practice.

In this section, studies of pharmacotherapies for posttraumatic cognitive impairments are organized according to medication class. Included in the discussion of the agents are the types of cognitive impairments they appear to improve. These studies include some double-blind placebo-controlled studies, uncontrolled open-label studies, and also case series or single-case reports. The strength of the evidence they provide for the use of these agents in clinical practice is a matter of considerable debate, and most offer evidence sufficient to support the use of these agents only as treatment options for posttraumatic cognitive impairments. Guided by the published literature and our own clinical experience, we offer preliminary recommendations regarding the pharmacotherapy of posttraumatic cognitive impairments. However, we encourage clinicians to consider the application of these agents to the treatment of in an individual patient a matter of empiric trial, and we suggest that clinicians consider reviewing the articles referenced herein prior to using these agents in their clinical practice.

### **Psychostimulants**

The effects of psychostimulants such as methylphenidate and dextroamphetamine on central monoaminergic systems

are complex. Methylphenidate and dextroamphetamine increase the release of dopamine and norepinephrine and, at higher doses, block the reuptake of these monoamines. These agents also appear to inhibit monoamine oxidase, which in combination with their other effects increases the effectiveness of monoaminergic neurotransmission. The effect of increased catecholaminergic activity in the ascending reticular activating system, the striatum, and the several cortical-subcortical circuits appears to be an increase in arousal, speed of processing, and attention. Such agents may afford such benefits in both the acute inpatient rehabilitation and post-acute outpatient settings, and there are theoretical reasons to suggest that stimulants may also facilitate neuronal recovery after brain injury by a variety of dopaminergically-mediated mechanisms (174).

#### *Methylphenidate*

Evans et al. (1987) (175) performed a single-case controlled study of methylphenidate (.15 mg/kg BID and .3 mg/kg BID) in a 21-year old male with a remote severe TBI. They observed improvements on measures of sustained attention, processing speed, motor speed, memory, and also mood. Subsequently, Gualtieri and Evans (1988) (176) performed a double-blind placebo-controlled crossover design study of methylphenidate among 15 adult patients with severe TBI. Subjects were 5–12 months post-injury, and were treated with methylphenidate .15 mg/kg BID and .3 mg/kg BID. They report treatment-related mood and behavioral, but not cognitive, improvements. In a similarly designed study, Speech et al. (1993) (177) treated 12 adult subjects with moderate to severe TBI with methylphenidate .3 mg/kg BID one year or more after their injuries. They observed a nonsignificant trend towards improvement in mood and performance on measures of vigilance and distractibility. They observed no improvements in memory, processing speed, or social interaction.

Plenger et al. (1996) (178) demonstrated a significant effect of methylphenidate on attention, Disability Rating Scale scores, and motor performance during subacute recovery from TBI in a randomized, double-blind, placebo-controlled study during which 23 subjects were treated for 30 days. They found that attention and functional performance were significantly improved by treatment with methylphenidate at day 30, but were not different from placebo treatment at day 90. In this study, methylphenidate treatment did not affect the ultimate level of recovery on these measures but appeared to improve the rate of recovery. However, analysis of data from this study is complicated by subject dropouts: only 12 subjects remained in the study at 30 days and only 9 subjects remained at 90 days. Consequently, it is difficult to fully evaluate the effects of methylphenidate in this

cohort. Whyte et al. (2002) (136) suggest that random variations in initial injury severity of these subjects might either account for or potentially mask true drug effects. In a similar study, Kaelin et al. (1996) (179) describe the effect of methylphenidate 15 mg twice daily on the course of recovery in 11 patients with TBI during acute inpatient rehabilitation setting. Using an A-A-B-A design, they demonstrated that methylphenidate significantly improved attention as measured by performance on digit span and symbol search tasks and was associated with improved Disability Rating Scale scores. Although one subject was withdrawn from the study due to tachycardia, methylphenidate was generally well tolerated. Although these studies are not without methodological problems and their findings are modest, they suggest that methylphenidate may improve cognitive function and the rate of recovery following TBI.

More recently, Whyte et al. (1997) (135) performed a randomized, double-blind, placebo-controlled, repeated crossover design to assess the effect of methylphenidate on attention in 19 subjects with nonpenetrating TBI recruited from either inpatient or outpatient settings. Referral for study participation was based on attending physician's recommendation of this treatment for clinically apparent problems with attention. Subjects were excluded if they had a history of prior TBI or other neurological disease, major mental illness, learning disability, attention deficit disorder, or if they were taking any psychoactive medication other than carbamazepine (which two subjects were taking at the time of study). Eleven of these patients participated in a task assessing distractibility and phasic arousal and 19 participated in an assessment of behavioral inattention. Patients were on average 31 years old (median age 27), had an average of 12 years of education, and were in general in the post-acute period following TBI (mean interval since injury = 514 days, median interval since injury = 145 days). Subjects underwent six serial assessments, typically separated by 1–3 days. Task administration was randomly assigned to methylphenidate or placebo in pairs over the course of the study in order to facilitate interpretation of individual subject performance patterns and to distinguish practice from treatment effects. Methylphenidate was administered at a dose of 0.25 mg/kg (rounded to the nearest 2.5 mg) BID, and assessments were performed approximately 90 minutes after administration of methylphenidate or placebo. The study tasks created 22 performance variables for analysis. Methylphenidate significantly improved arousal and speed of processing, but did not improve most aspects of vigilance (sustained attention), distraction, or motor speed.

Placed in the context of other studies of methylphenidate in adults with posttraumatic cognitive impairments, the findings of Whyte et al. (135) suggest that principal benefit of this agent is on processing speed and to a lesser extent on subjective ratings of behavior and

mood. This finding stands in contrast to the more common clinical use of methylphenidate for impairments of vigilance and distractibility. They note that there is, at present, little data to support the use of methylphenidate for posttraumatic memory impairments. It stands to reason that improvements in attention might secondarily benefit memory, although the studies performed to-date offer little support for this suggestion. Whether methylphenidate has benefits on aspects of attention other than processing speed remains uncertain, but common clinical experience suggests that at least some persons with attentional impairments benefit from treatment with this agent.

Two studies (180, 181) describe the use of methylphenidate in the treatment of children and adolescents with posttraumatic cognitive impairments. In the study by Mahalick et al. (1998) (180), methylphenidate .3 mg/kg BID was administered in a crossover design study of 14 subjects (age 5–14 years) approximately 1.2 years after mild-to-moderate TBI. They observed statistically significant improvements in vigilance, processing speed, and distractibility. In a similarly designed study, Williams et al. (1998) (181) examined the effects of methylphenidate 5–10 mg BID (adjusted for subject weight) in 10 subjects (age 5–16 years) who were on average 2 years post-injury (of unspecified severity). They observed no significant effects of this treatment on cognition, although there was suggestion in their data of improved accuracy on a continuous performance task. They report a trend towards behavioral improvements as assessed by teachers using the Conners Rating Scale (a scale commonly used in the assessment of children with attention deficit disorder), but parents ratings on this scale did not support teacher ratings. Considered together, these studies leave uncertain the possible benefits of methylphenidate in children and adolescents with posttraumatic cognitive impairments.

### *Dextroamphetamine*

Dextroamphetamine is frequently used in the treatment of attention and memory impairment following TBI, and is thought to have additional beneficial effects on depression, anergia, and impaired motivation. However, there are only three reports to support its use in this population. Evans and Gualtieri (1987) (176) assessed cognition, mood, and behavior during treatment with dextroamphetamine .1 mg/kg BID and .2 mg/kg BID. They describe treatment-related improvement in measures of vigilance (sustained attention), processing speed, motor speed, memory, and mood during treatment with dextroamphetamine. Bleiberg et al. (1993) (173) conducted a double-blind, crossover study of the effects of dextroamphetamine, lorazepam, and placebo on measures of processing efficiency and speed in a 55-year old male who suffered a complicated mild TBI (5 minutes loss of consciousness and left subdural hematoma) approximately



5 years prior to study. They observed improvements in cognitive speed and stability of performance (correct responses per unit of time) during treatment with dextroamphetamine but not placebo, and also observed decrements in cognitive function during treatment with lorazepam. Hornstein et al. (1996) (182) reviewed the use of dextroamphetamine in the treatment of individuals during acute rehabilitation after TBI in the context of a larger review of this subject. Of the 27 patients so treated, 15 appeared to benefit from treatment with dextroamphetamine as measured by Glasgow Outcome Scale.

### *Methylphenidate and Dextroamphetamine in Clinical Practice*

Although psychostimulants would be predicted to improve catecholaminergically-dependent cognitive functions among persons with TBI, the literature is variable with respect to their beneficial effects. In light of the relative lack of *in vivo* evidence of long-term dopaminergic or noradrenergic dysfunction following TBI presented earlier in this chapter, the variability of benefit in the published reports is not surprising. Additionally, methodological issues (e.g., small sample sizes, study design, assessment measures, study period, interval since injury, etc.) in the studies performed to-date make interpretation of the cognitive and neurobehavioral benefits of psychostimulants in persons with TBI difficult, at best. Nonetheless, common clinical experience suggests that some patients do experience cognitive improvements during treatment with psychostimulants. To the extent that an individual's posttraumatic cognitive impairments are related to catecholaminergic dysfunction, whether from injury to afferent projections, synaptic catecholamine metabolism (i.e., COMT enzymatic activity) that exceeds catecholamine availability, or some combination of these factors, methylphenidate and related psychostimulants may afford some degree of cognitive improvement among persons with TBI, and may in particular be useful for the treatment of posttraumatic impairments in arousal, speed of processing, and possibly attention.

In clinical practice, careful assessment of arousal, speed of processing, and attention should be undertaken before and during treatment with these agents. Although such assessments may be difficult to undertake in some clinical practices (183), they are important to perform in order to determine whether these medications impart sufficient benefit to merit their continued use in a given patient. Assessment with appropriate neuropsychological tests (for example, continuous performance tests or other standardized tests of reaction time or processing speed) may be particularly helpful in this regard. In the absence of improvement on such measures during treatment with these agents, reports of subjective improvement in cognition or daily function during treatment with these

agents are frequently used as a measure of treatment response. While such reports may be used to justify continued use of these agents, the observation of subjective improvement but lack of improvement on objective measures should prompt reconsideration of the etiology of the impairments reported. Since psychostimulants may improve mood, increase motivation, or lessen fatigue, subjective improvements without evidence of demonstrable cognitive improvements may suggest that the primary problem lies in posttraumatic depression, apathy, fatigue, or some combination of these non-cognitive problems.

Unlike many other medications used to treat neuropsychiatric conditions, stimulants generally take effect quickly (within 0.5–1 hour following administration) and also lose effect after only a few hours. Therefore, the first issue in the administration of these agents is determining the optimally effective dosage and dosing frequency required to sustain that effect. Methylphenidate and dextroamphetamine are generally administered twice daily, typically at breakfast and again at midday. Initial dosing with either agent generally begins at 5 mg BID and is gradually increased in increments of 5 mg BID until either beneficial effect or medication intolerance is achieved. Most studies suggest that optimal doses of either methylphenidate or dextroamphetamine are in the range of 10–20 mg BID, although some clinicians use of considerably higher doses (i.e., 40 mg or more BID). Some individuals may require relatively frequent dosing (i.e., readministration every 3–4 hours) of methylphenidate or dextroamphetamine in order to sustain cognitive benefits from them throughout the course of the day. Multiple longer-acting methylphenidate or dextroamphetamine preparations are available. Individuals requiring relatively high and frequent doses of methylphenidate or dextroamphetamine may benefit from use of longer-acting preparations of these medications.

Adverse reactions to these medications are most often related to increases in cerebral dopamine, and to a lesser extent cerebral norepinephrine, activity. Dextroamphetamine and methylphenidate have the potential to produce paranoia, dysphoria, anxiety, agitation, and irritability, although these adverse effects are in practice very uncommon at doses typically used to treat posttraumatic cognitive impairments. Psychosis is a relatively rare consequence of administration of these medications. Even among persons with posttraumatic psychosis, these agents may be of benefit for cognitive impairments and without untoward effects on psychotic symptoms when used in combination with an atypical antipsychotic medication. However, combined therapy with psychostimulants and antipsychotics is not recommended unless the patient is under the care of a neuropsychiatrist with expertise in the use of this medication combination. Mild increases in heart rate and/or blood pressure may occur

during treatment with psychostimulants, although these tend to occur relatively infrequently in patients without other cardiac or vascular problems and are only rarely of sufficient magnitude to merit discontinuation of these agents. Use of these agents during pregnancy is discouraged, and their use is contraindicated among patients receiving monoamine oxidase inhibitors (MAOIs) and women who are breastfeeding. Clinicians are advised to avoid use of these agents among persons with comorbid Tourette's syndrome and other tics, glaucoma, untreated hypertension or cardiovascular problems, and symptomatic hyperthyroidism. These agents may potentiate the effects of phenobarbital and phenytoin by delaying gastrointestinal absorption, increase the noradrenergic effects of tricyclic antidepressants, increase the dopaminergic effects of antiparkinsonian agents, and potentiate the analgesic properties of meperidine. Because depressed mood and increased fatigue may develop following abrupt discontinuation of psychostimulants, these medications should be discontinued gradually among patients receiving them chronically.

Clinicians are sometimes reluctant to make use of psychostimulants out of concern that they might lower seizure threshold in patients with TBI. Wroblewski et al. (1992) (184) examined changes in seizure frequency after initiation of methylphenidate among 30 patients with both severe brain injury and posttraumatic seizures. The frequency of seizures was monitored for 3 months before treatment with methylphenidate, 3 months during treatment, and 3 months after treatment was discontinued. They found that only 4 patients experienced more seizures during methylphenidate treatment, and 26 had either fewer or the same number of seizures during treatment. Although many patients in this study were treated concurrently with anticonvulsant medications, 13 of these experienced fewer seizures when treated with methylphenidate. While this finding should not be misunderstood as suggesting an anticonvulsant effect of methylphenidate, it does suggest that methylphenidate does not substantially increase seizure risk among persons with TBI, including those with posttraumatic epilepsy.

Similarly, in a double-blind placebo-controlled study of the effects of methylphenidate (0.3 mg/kg body weight bid) in 10 children with well-controlled seizures and attention-deficit disorder, no seizures occurred during the 4 weeks of treatment with either active drug or placebo (185). Although this observation was not made among persons with TBI, it supports the thesis that methylphenidate itself does not appear to increase the risk of seizure even among patients with established epilepsy. Interestingly, dextroamphetamine has been used adjunctively in the treatment of refractory seizures (186). While most clinicians would not regard this agent as an adjunctive therapy for seizures, this report echoes other observations of a relative lack of adverse effect of stimulants

on seizure frequency. It appears that this class of medications is generally well tolerated with respect to its effects on seizure frequency, and that even established epilepsy should not preclude treatment with this agent when a clinician deems it to be of potential benefit to an individual patient.

### **Bromocriptine**

Bromocriptine appears to act directly on postsynaptic dopamine receptors – particularly dopamine type 2 (D2) receptors – and serves as an agonist in dopaminergically-mediated cerebral systems. At low doses, bromocriptine acts as a pre-synaptic D2 agonist, and thereby reduces dopaminergic release and function in dopaminergically-mediated systems. Its net effect at mid-range doses appears to be augmentation of cerebral dopaminergic systems (187). Accordingly, Eames (1989) (188) suggest that bromocriptine may be useful in treating “cognitive initiation” problems of brain injury patients who are at least 1 year post-injury. McDowell et al. (1998) (189) studied 24 subjects using a counterbalanced, double-blind, placebo-controlled crossover design. Bromocriptine improved performance on some frontally-mediated tasks, such as executive function and dual-task performance, but did not improve working memory. No other effects of bromocriptine on posttraumatic cognitive dysfunction were observed.

Others report benefits on nonfluent aphasia (71), akinetic mutism (190), and apathy (191) during treatment with this bromocriptine among patients with such problems following stroke. These effects have been attributed to dopaminergic augmentation of frontal function (192). Unlike the psychostimulants, bromocriptine has not been demonstrated to have a consistent effect on affective lability or mood disorders due to TBI, stroke, or other neurological conditions.

Treatment with this agent generally begins with 2.5 mg/day and is gradually titrated to the highest dose tolerated. Common side effects during treatment with bromocriptine include dizziness, drowsiness, faintness, syncope, nausea, vomiting, abdominal cramps, constipation, and diarrhea, although these are generally of mild severity. Uncontrolled hypertension and hypersensitivity to ergot alkaloids are strict contraindications to the use of bromocriptine. Although use of this agent among women who are breastfeeding their infants is contraindicated, use during pregnancy does not appear to be associated with significant increased adverse events among pregnant patients or on fetal development. It has been suggested that bromocriptine may possess some anticonvulsant properties (193). Although this suggestion should not be misunderstood as an endorsement of bromocriptine for the adjunctive treatment of posttraumatic epilepsy, it may offer some reassurance of its safety

for use among cognitively impaired TBI survivors with this problem.

### Amantadine

The effects of amantadine on dopaminergic function are not entirely clear, but include increasing dopamine release, decreasing presynaptic dopamine reuptake, stimulation of dopamine receptors, and/or enhancement of postsynaptic dopamine receptor sensitivity. As such, amantadine is generally regarded as an agent whose principal effects on posttraumatic cognitive and neurobehavioral disturbances are mediated through indirect augmentation of dopaminergic function. As noted previously, amantadine is an uncompetitive antagonist at NMDA receptors (194). The clinical effects of amantadine's NMDA receptor antagonist properties are uncertain, although it is possible that it may contribute to stabilization and/or augmentation of glutamatergic function. Additionally, amantadine also appears to stimulate striatal acetylcholine release indirectly via its effects on NMDA receptors in this brain region. To the extent that improved striatal cholinergic function contributes to improvements in cognition dependent on frontostriatal circuits, amantadine might also be of benefit via this mechanism of action. However, the relative contributions of NMDA receptor antagonism and/or indirect striatal pro-cholinergic effects to the clinical effects produced by amantadine are at present a matter of speculation.

Kraus and Maki (1997) (125) administered amantadine 400 mg/day to six patients with TBI and observed improvements in motivation, attention and alertness, and executive function. They also observed treatment-related improvements in impulsivity and emotional (affective) lability. It has also been suggested that amantadine improve posttraumatic anergia, abulia, mutism, anhedonia, perseveration, and/or agitation (126–129).

Amantadine is often started at a dose of 50 mg BID, and is usually increased every week by 100 mg/day to either symptomatic improvement or medication intolerance. In the experience of the authors, amantadine may be of use in the treatment of hypoarousal and/or fatigue following TBI. Amantadine 100 mg BID is often sufficient to impart improvement in these symptoms without undue side effects. When higher doses are necessary, the maximum dosage of amantadine should not exceed a total daily dose of 400 mg. When used at higher doses, treatment-emergent adverse effects may be more common.

Headache, nausea, diarrhea, constipation, anorexia, dizziness, lightheadedness, orthostatic hypotension may occur during treatment with amantadine. Anxiety, irritability, depression, and hallucinations may also develop during treatment with this agent, but are relatively uncommon. At higher doses, psychosis and confusion may occur. These treatment-emergent symptoms may be

the result of excessively strong NMDA receptor antagonism, dopaminergic excess, or some combination of these effects. Abrupt withdrawal has been associated (rarely) with neuroleptic malignant syndrome. Adverse reactions to amantadine appear to occur more often in elderly patients than in younger patients. Additionally, coadministration of triamterene/hydrochlorothiazide may decrease renal excretion of amantadine, resulting in medication intolerance at doses that would ordinarily be regarded as within the usual therapeutic range.

Although amantadine does not possess direct anticholinergic activity *per se* at conventional therapeutic doses, it is not uncommon for patients treated with this agent to develop anticholinergic-like symptoms. Additionally, amantadine may potentiate the effects of anticholinergic agents and other psychostimulants. These observations leave open the question of amantadine on cholinergic function *in vivo*, as the basic science studies of the neurotransmitter effects of this agent would not predict these effects.

It has been reported that amantadine may lower seizure threshold (128). However, this suggestion is contentious. Two studies (195, 196) investigated amantadine as an adjunctive anticonvulsant therapy among persons with refractory epilepsy. These studies report improved seizure control in about 30%, no change in seizure frequency in 30–40%, and worsened seizures in 20–30% among patients treated with amantadine. These findings suggest that amantadine does not invariably precipitate or worsens seizure frequency, even among persons with refractory epilepsy. Nonetheless, it is prudent to be vigilant for the development or worsening of seizures when amantadine is used among persons with TBI.

### Carbidopa/L-Dopa

L-dopa (levodopa) is a dopamine precursor. When coupled with carbidopa to decrease the extent of its metabolism in the periphery, L-dopa increases dopamine levels in the central nervous system. Although this medication is uncommonly used in clinical practice for these purposes, it may be an alternative to the traditional psychostimulants for the treatment of cognitive impairments and other neurobehavioral disturbances following TBI.

Lal et al. (1988) (197) describe the use of carbidopa/L-dopa among 12 patients with brain injury (including several patients with hypoxic-ischemic brain injuries). During treatment with L-dopa/carbidopa 10/100 to 25/250 QID, patients demonstrated improvements in alertness and concentration, decreased fatigue, hypomania, and sialorrhea, as well as improved memory, mobility, posture, and speech.

Treatment with carbidopa/L-dopa should begin with low doses (10/100 BID) and may be gradually increased to doses of 25/250 QID. Consultation with a neurologist or neuropsychiatrist experienced in the use of this

agent in this population is suggested when clinicians unfamiliar with carbidopa/L-dopa elect to use this agent in this population. Common side effects are predominantly related to its central dopaminergic effects, and may include dyskinesias, anxiety, hallucinations (especially visual), paranoia or overt psychosis. Nausea may be a treatment-limiting side effect in some patients, and is more common during treatment with preparations with relatively lower doses of carbidopa (i.e., 10/100 vs. 25/100). Other less frequent side effects include palpitations, orthostatic hypotension, anorexia, vomiting, and dizziness. Rare but serious adverse effects include gastrointestinal hemorrhaging, duodenal ulcer, hypertension, phlebitis, leukopenia, agranulocytosis, thrombocytopenia, and hemolytic or nonhemolytic anemia. Carbidopa/L-dopa does not appear to reduce seizure threshold clinically, but there is insufficient data with which to assess the risk of seizures during treatment with this agent among persons with TBI.

### Modafinil

Modafinil, a medication recently approved for the treatment of excessive daytime somnolence in patients with narcolepsy, may have a role in treatment of post-TBI fatigue and cognitive impairment. Although the exact mechanism of action of modafinil is not fully understood, animal studies suggest that its promotion of wakefulness may be attributable to activation of hypocretin (orexin) neurons in the lateral hypothalamus (198), indirect, dose-dependent reduction GABA release in the cerebral cortex, medial preoptic area, and posterior hypothalamus (199, 200), and dose-dependent increases in glutamate release in the ventrolateral and the ventromedial thalamus (201). Some combination of these mechanisms in humans may increase arousal via activation of neurons of the arousal system, either directly via glutamatergic thalamic activation, indirectly via reduction of GABA function, or through the secondary effects of lateral hypothalamic projections to regions involved in control of arousal and sleep-wake cycle (tubero-mammillary nucleus and the locus coeruleus) (202).

Studies of the effect of modafinil on fatigue and excessive sleepiness in patients with multiple sclerosis (203, 204) and Parkinson's disease (205) suggest that the beneficial effects of this agent are not exclusive to narcolepsy. Elovic (2000) (206) has suggested that modafinil may be of similar benefit in patients with TBI. Teitelman (2001) (207) described his use of modafinil among 10 outpatients with nonpenetrating traumatic brain injury and functionally significant excessive daytime sleepiness and in two patients with somnolence due to sedating psychiatric medications. The patients included in his report were between the ages of 42 to 72 years, all were outpatients, and were treated in an open-label fashion.

Doses of modafinil ranged between 100 mg to 400 mg daily. Nine patients reported marked improvements in excessive daytime sleepiness and three reported moderate improvements. Some of these patients reported subjective improvements in attention as other cognitive functions. Although this medication was generally well tolerated, Teitelman (2001) (207) observed treatment intolerance due to increased "emotional instability" in two women with brain injury complicated by multiple other medical conditions who were receiving multiple additional medications.

At the time of this writing there are no published formal clinical trials with which to evaluate the effectiveness or tolerability of modafinil for post-traumatic hypoarousal, hypersomnolence, fatigue, or other cognitive impairments. We have used this agent in the acute inpatient rehabilitation setting in persons with moderate-to-severe TBI in the lower Rancho Los Amigos stages (III-IV) for the treatment of hypoarousal or excessive daytime sleepiness with some success and without serious adverse effects; however, anecdotal reports such as this must be regarded with caution pending further study of this agent for this purpose.

If used in this population, modafinil should be started at 100 mg QAM, and can be increased to up to 400 mg/day administered in either a single daily dose or two divided doses (i.e., 200 mg in the morning, and 200 mg in the early afternoon). Higher doses (up to 600 mg daily) are sometimes used, but there is no evidence in any patient population that such doses offer benefit beyond that achieved with 400 mg daily.

### Other Stimulant-like Medications

In general, prescription of tricyclic antidepressants should be avoided where possible among persons with significant posttraumatic cognitive impairments. The significant anticholinergic and antihistaminergic effects of these agents would be expected to further impair cognition in this population; such adverse effects of tricyclic antidepressants have been reported among persons with TBI and other neurologically-impaired populations (208, 209). Protriptyline, a secondary amine tricyclic agent, may be an exception in this regard. This agent has been suggested to have sufficient stimulant properties to permit its use for anergia and diminished motivation in TBI patients (210). However, this agent does not appear to confer any benefit on cognition beyond that afforded by improved arousal and motivation alone. Protriptyline should be considered as a treatment for posttraumatic hypoarousal, anergia, and apathy only when other standard psychostimulants have not proven effective or have produced intolerable side effects. Similarly, Reinhard and colleagues (1996) (211) administered amitriptyline (1 patient) and desipramine (2 patients) and found improvement in arousal and initiation after TBI. They

hypothesized that the cognitive-enhancing effects of these agents resulted from the pro-noradrenergic effects of these agents. Again, these agents may be of some benefit on posttraumatic impairments in arousal but are probably best regarded as treatments of last resort when other stimulants have proven ineffective or intolerable. The side effects and drug-drug interactions of these agents are discussed in more detail in Chapter 52 (Pharmacotherapy of Neuropsychiatric Disturbances).

Showalter and Kimmel (2000) (212) report better-than-expected improvements in level of arousal in 9 of 13 severe (Rancho Los Amigos Scale I-III) TBI patients taking lamotrigine during the post-acute recovery period (up to 10 months). They suggested that this agent may permit more rapid emergence from deeper stages of diminished arousal (i.e., coma) following TBI than might occur spontaneously. Pachet et al. (2003) (213) also report improvements in cognition and other neurobehavioral functions (as assessed by the Functional Independence Measure) in a single case study of this agent in a 40 year-old man with severe TBI treated with lamotrigine for approximately four months in the late (1–1.5 years) period following his injury. The mechanism by which lamotrigine confers such benefits is unclear. Showalter and Kimmel (2000) (212) suggest that lamotrigine's ability to block of sodium channels and inhibit glutamate release may either prevent excitotoxic injury and/or facilitate recovery from injury. Additional studies are needed to ascertain the validity of this suggestion.

### Cholinesterase Inhibitors

As described earlier in this chapter, posttraumatic cognitive impairments may, at least in part, result from chronic deficiencies of cerebral cholinergic function (7, 214). The common clinical observation of the susceptibility of TBI patients to exacerbation of cognitive impairments during treatment with anticholinergic medications, as well as animal studies echoing this observation (155, 159, 215), suggests that TBI results in reduced reserves of cerebral acetylcholine. As such, augmentation of cholinergic function may be an effective strategy by which to improve posttraumatic cognitive impairments.

Administration of the acetylcholine precursors, lecithin and choline, do not appear to reliably increase cerebral cholinergic function or confer cognitive benefits among persons with other neurological illnesses in which cholinergic deficits figure prominently (e.g., Alzheimer's disease) (216). Additionally, centrally-selective nicotinic or muscarinic receptor agonists are not presently available for use in this context.

At present, the principal pharmacologic means by which central cholinergic function may be augmented is cholinesterase inhibitors, of which there are several available for use in humans. These include physostigmine,

tacrine, donepezil, rivastigmine, and galantamine. Although these agents differ in their central (i.e., cerebral) selectivity and additional mechanisms of action – for example, prominent butyrylcholinesterase inhibition by rivastigmine (217), and allosteric nicotinic modulation by galantamine and physostigmine (218) – all of these agents principally exert their clinical benefits via inhibition of synaptic acetylcholinesterase. This enzyme is the predominant synaptically-active cholinesterase, and is the principal mechanism by which acetylcholine is metabolized in cerebral synapses. Inhibition of synaptic acetylcholinesterase increases the availability of acetylcholine to both pre- and post-synaptic nicotinic and muscarinic receptors, and may thereby improve cholinergically-dependent cognitive functions such as arousal, attention, memory, language, and executive function.

Although there is considerable interest in the possible use of the cholinesterase inhibitors for the treatment of posttraumatic cognitive impairments, at the time of this writing there is published data for only physostigmine and donepezil. It is possible that the secondary mechanisms of action of both rivastigmine and galantamine may confer either greater or additional benefits on cognitive and neurobehavioral function among persons with TBI; however, reports describing both their effects and tolerability are needed before offering any formal recommendations regarding their use in this population.

### *Physostigmine*

Physostigmine inhibits acetylcholinesterase both centrally and peripherally. Although it exerts its principal effects through inhibition of synaptic acetylcholinesterase, it also appears to allosterically modulate nicotinic receptors in a fashion similar to galantamine (218). Several reports describe cognitive improvements following administration of physostigmine, both in the acute (219) and post-acute (220, 221) injury period. Levin et al. (1986) (222) performed a double-blind, placebo-controlled study of combined oral physostigmine and lecithin in 16 patients with cognitive impairment following moderate to severe TBI. Sustained attention on the continuous performance test was more efficient under physostigmine than placebo, and lecithin did not appear to increase this effect. Cardenas et al. (1994) (223), in a double-blind, placebo-controlled, crossover design study of physostigmine, placebo, and scopolamine (a muscarinic receptor antagonist) in 36 males with memory impairment of at least 3 months duration following TBI, demonstrated improved memory scores on the long-term storage component of the Selective Reminding Test in 44% of subjects during treatment with oral physostigmine but not placebo or scopolamine.

Physostigmine is available in oral and intravenous preparations. Its absorption after oral administration is unpredictable, and its duration of action ranges from

30 minutes to 5 hours. Consequently, its use entails frequent dosing. Although physostigmine may be of benefit to cognitively impaired TBI survivors, both its lack of central selectivity and frequent administration produce systemic toxicity that limits its acceptability as a treatment for posttraumatic cognitive impairments (224). Given the availability of newer and generally better-tolerated cholinesterase inhibitors, we do not recommend routine use of physostigmine among persons with TBI. However, the benefits afforded by this agent do support the suggestion that cholinesterase inhibition may improve posttraumatic cognitive impairments in some patients, and may be used to support the use of the newer cholinesterase inhibitors in this population.

### *Donepezil*

Donepezil is a cholinesterase inhibitor that exhibits relative central selectivity. Although it modestly inhibits butyrylcholinesterase (225), its predominant mechanism of action is believed to be inhibition of synaptic acetylcholinesterase (226). Taverni et al. (1998) (227) describe improvements in refractory memory impairments on the Rivermead Behavioral Memory Test and Ross Immediate Processing Assessment in the late (>3 years) post-injury period in two patients with severe TBI. These benefits were apparent after approximately three weeks of treatment with donepezil 5 mg per day. In a similarly small case series, Masanic et al. (2001) (228) treated four patients with persistent posttraumatic cognitive and neurobehavioral impairments with donepezil 5 mg per day for eight weeks followed by treatment with donepezil 10 mg per day for an additional four weeks. Patients were assessed pre- and post-treatment using the Rey Auditory Verbal Learning Test (RAVLT) and the Complex Figure Test (CFT). Items from the Rivermead Behavioral Learning Test (RBMT) and a test of semantic fluency were also administered. The Neuropsychiatric Inventory (NPI) was used to assess other neurobehavioral changes during treatment, and overall function was assessed using a clinician-based rating scale and the Functional Independence Measure (FIM). The authors reported modest but significant improvements in learning and short- and long-term recall on the RAVLT and more substantial improvements in short- and long-term recall on the CFT. Trends toward improvements were observed on the RBMT and the NPI. Given the small sample sizes, remoteness of injury, and the relatively severe injuries of the subjects in both studies, the observation of improvement in is encouraging of the possible benefits of donepezil for the treatment of posttraumatic memory impairments. However, the small sample sizes and uncontrolled nature of both studies limits the validity and generalizability of these treatment effects.

Kaye et al. (2003) (229) performed an 8-week open-label study of 10 persons with remote (1–5 years,

mean = 1.2 years) TBI in an outpatient setting using a forced titration protocol (5 mg per day for 4 weeks followed by 10 mg per day for 4 weeks). Subjects ranged in age from 26–60 years (mean age = 41 years), and included six with mild, one with moderate, and 3 with severe TBI. All subjects underwent pre- and post-treatment neuropsychiatric evaluations, including assessment of cognition using the Global Memory Scale (GMS) of the Memory Assessment Scale and two-independent clinician ratings of overall improvement using the Clinical Global Improvement scale (CGI). Eight subjects completed the study; one subject was dropped from the study due to treatment noncompliance, and one subject discontinued treatment due to intolerable gastrointestinal side effects. Among those completing the study, CGI ratings improved, although not necessarily as a function of improvements in memory. In fact, the authors observed no improvement on the GMS. Instead, the authors report that CGI improvements instead appeared to reflect the subject reports of improvements in “focus, attention, and clarity of thought.” They note that several subjects reported being better able “to keep multiple ideas in mind simultaneously,” and that subjects’ family members frequently described “improved socialization.” The authors note the limitations of the cognitive assessment used as a primary outcome measure in this study, and suggest that other measures better suited to assess cognitive flexibility, non-verbal abstract reasoning, learning from mistakes, and incidental visual memory might be more appropriate outcome measures in subsequent studies of this kind. They acknowledge that controlling for other variables such as age, severity of injury, time since injury, and baseline cognitive function, as well as the use of placebo control, is necessary to more rigorously assess the benefits of donepezil in the treatment of posttraumatic cognitive impairments. In spite of these limitations, they conclude their report by noting that seven of the eight subjects completing the study elected to continue treatment with donepezil given the subjective improvements they experienced during its use in this study. The eighth subject also reported such benefits, but elected not to continue treatment due to the development of treatment-emergent nausea.

Morey et al. (2003) (230) studied the effectiveness of donepezil for the treatment of chronic memory impairments in a group of seven patients with TBI. Subjects were on average 33 months post-injury (range = 20–65 months) and mean age was 31 years (range = 19–51). All subjects were without other medical, psychiatric, or physical problems that might interfere with ability to participate in neuropsychological assessment, and none were taking medications with anticholinergic properties. Measures of cognitive function included the Brief Visual Memory Test – Revised, Hopkins Verbal Learning Test, Digit Span and Letter-Number Sequence subtests of the Weschler Adult Intelligence Scale – Revised, Controlled Oral Word

Association Test, and the Memory Functioning Questionnaire, all of which were administered pre- and post-treatment during the two treatment phases of the study. These phases included donepezil 5 mg daily one month followed by donepezil 10 mg daily for an additional five months; following a six-week washout period, patients were treated for an additional six months with donepezil 5 mg daily. Treatment-emergent side effects (lethargy and somnolence) were observed in two subjects, prompting their discontinuation from the study. It is not clear in this report whether the final subject group in who cognitive testing was performed included seven or five subjects. Regardless, there were very few other complaints of side effects at either dose of donepezil. Improvements in immediate and delayed memory as assessed by the Brief Visual Memory Test – Revised were reported as a function of treatment with donepezil 10 mg per day but not 5 mg per day. No other significant effects on cognition were observed during treatment with this agent at either dose. Although this report suggests the possibility of benefit on visual memory during treatment with donepezil at 10 mg per day, lack of subject characterization data (i.e., severity of injury, presence of focal contusions vs. diffuse injury) and small sample size limit the generalizability of both positive and negative findings of this study.

Whelan et al. (2000) (231) performed an open-label study of donepezil in 53 outpatients and subsequent cognitive impairment who were receiving treatment for neuropsychiatric problems following TBI. All patients were assessed pre- and post-treatment using a clinician-based rating scale. Twenty-two of these patients were also assessed pre- and post-treatment using the Wechsler Adult Intelligence Scale-Revised (WAIS-R) and the Hooper Visual Organization Test. All of the patients were treated adjunctively with donepezil 5–10 mg daily for an average of 12 months. The authors reported improvements in full-scale IQ in the subset of patients in who cognitive assessments were performed, and improvements in clinician-based ratings in the sample as a whole. Although these improvements occurred well after the period during which spontaneous recovery and “practice effects” might offer better explanations for them, details regarding injury severity, specific neuropsychiatric comorbidities, other concurrent treatments, and changes in those treatments during the period of study are not fully described in that report, making interpretation of the reported findings challenging. Additionally, the cognitive assessment measures used are unusual in treatment studies of this kind. It is possible that modest improvements across the range of cognitive functions assessed by the WAIS-R contributed to the observed improvements while improvements in subscale scores were insufficient to rise to statistically significant levels. Alternatively, the sample size may have been inadequate to provide the statistical power needed to demonstrate a significant effect of

donepezil on the WAIS-R subscales. Given these considerations, this study is probably best interpreted as offering only a suggestion of a possible benefit of donepezil as an adjunctive treatment for persistent cognitive impairments among persons with other chronic neuropsychiatric disturbances following TBI.

More recently, Zhang et al. (2004) (232) reported findings from a 24-week, randomized, placebo-controlled, double-blind crossover trial of donepezil 10 mg daily in 18 subjects with TBI seen in two University-based hospitals. Patients were enrolled on the basis of a documented history of TBI (regardless of severity) 2–24 ( $4.6 \pm .7$ ) months prior to the study. Approximately two-thirds of the patients were male, ranged in age from 19–49 years, and had 10–17 years of education. Mean GCS scores at 24–48 hours post-injury were approximately  $9 \pm 1$ . All subjects demonstrated persistent attention as measured by the Paced Auditory Serial Addition Test (PASAT) and/or short-term memory impairment as measured by the Auditory Immediate Index (AII) or Visual Immediate Index (VII) of the Weschler Memory Scale-III. Subjects were excluded if they had cardiac arrhythmias on electrocardiogram (regardless of etiology), a history of cardiac contusion, uncontrolled posttraumatic seizures, uncorrected electrolyte imbalance, endocrine dysregulation, infection, or gastrointestinal bleeding. Subjects with severe cognitive and behavioral disturbances (i.e., Rancho Los Amigos functioning at level V or below), other neurologic or psychiatric problems (e.g., stroke, epilepsy, major depression, or neurodegenerative disorders), taking other psychotropic medications (e.g., antidepressants, anticonvulsants, antipsychotics, psychostimulants), or communication impairments (aphasia, dysarthria) that would interfere with neuropsychologic testing were excluded. Glasgow Outcome Scale scores were 4 or 5, and Rancho Los Amigos scores ranged from 7 to 8. In other words, the majority of subjects were functioned at an independent or a modified independent level but required some guidance and supervision from family members for daily activities.

Subjects were randomly assigned to two study groups consisting of 10 subjects each. The first group received donepezil 5 mg daily for two weeks followed by donepezil 10 mg daily for an additional 8 weeks; after a 4 week washout period, patients received placebo for 10 weeks. The second group received these preparations in the opposite order. Subjects were assessed using the PASAT, AII, and VII at baseline, and again at treatment weeks 10 and 24. Both study groups demonstrated significantly improved performance on these measures at treatment week 10 compared with baseline, and both groups demonstrated improvements at treatment week 10 compared to placebo week 10. The group treated with donepezil prior to placebo also demonstrated cognitive improvements at the end of the placebo phase when compared to baseline,

suggesting a possible carry-over effect of donepezil on cognitive performance in this study population.

Although this is the most carefully performed study of donepezil for attention and memory impairments following TBI to-date, it suffers from several limitations. First, subjects were studied during the period in which spontaneous recovery may occur; while the placebo-controlled crossover design of the study offers some control over this confound, it cannot be entirely discounted as a contributor to the improvements observed in these subjects. Second, subjects with either mild injuries or more severe cognitive impairments were excluded from the study, limiting the generalizability of the study findings. Similarly, patients with common medical and neuropsychiatric comorbidities were excluded, as were patients taking other neuroactive medications prescribed commonly in this population. Both of these exclusions also limit the generalizability of the study findings. Nonetheless, this study offers reasonably strong evidence that donepezil improves attention and memory impairments in the post-acute injury period.

### *Cholinesterase Inhibitors in Clinical Practice*

Collectively, these studies suggest that cholinesterase inhibitors may be of benefit for the treatment of post-traumatic cognitive impairments, and particularly post-traumatic attention and memory impairments. However, findings from the limited number of published studies are mixed with respect to the beneficial effects of these agents in this population. Given the ubiquitous role of acetylcholine in cognition and behavior, the cholinesterase inhibitors might be expected to improve a variety of cognitive impairments (e.g., hypoarousal, inattention, memory impairment, aphasia, executive dysfunction) and other neurobehavioral disturbances (e.g., apathy) in which cholinergic dysfunction is implicated.

The extent to which this type of treatment will be useful in an individual patient most likely depends on the extent to which cholinergic dysfunction in that patient contributes to his or her cognitive and behavioral impairments. Not all persons with TBI demonstrate post-mortem (16, 162, 163) or *in vivo* electrophysiologic (24) evidence of posttraumatic cholinergic dysfunction. Consequently, it is unlikely that augmentation of cerebral cholinergic function will benefit all persons with post-traumatic cognitive impairments. However, findings from the published studies of cholinesterase inhibitor therapy among persons with TBI suggest that at least a portion of this population will benefit from such treatments. Multicenter, double-blind, placebo-controlled trials are needed to define both the types of benefits afforded by such treatments and the clinical profile of TBI patients most likely to experience such benefits.

For the present, cholinesterase inhibitors are among the pharmacotherapeutic options available to clinicians

treating persons with posttraumatic cognitive impairments. Among these, donepezil is prescribed most commonly, although rivastigmine and galantamine are also sometimes used. When donepezil is prescribed, treatment begins with 5 mg daily. The relatively long half-life of donepezil makes it suitable for once-daily dosing (226). It is not clear whether increases to donepezil 10 mg daily affords additional benefits over 5 mg daily. When higher-dose donepezil is used, titration is generally undertaken at intervals of 2–4 weeks. Slower dose titration may limit the development of treatment-emergent side effects (usually gastrointestinal). Rivastigmine and galantamine have shorter half-lives, and require twice daily dosing. Rivastigmine is generally started at 1.5 mg BID and increased in 1.5 mg BID increments every four weeks until maximal benefits are attained or treatment intolerance develops. Galantamine is generally started at 4 mg BID and increased in 4 mg BID increments until maximal benefits are attained or treatment intolerance develops.

Although all of these agents may produce side effects such as headache, nausea, diarrhea, vomiting, fatigue, insomnia, muscle cramping, pain, and abnormal dreams, these side effects are generally related to overly rapid dose-escalation. Even in this context, such effects are usually transient. When intolerable side effects develop and/or persist during treatment with any of these agents, dose reduction is prudent. Such reductions may reduce adverse effects and permit patients to continue treatment. Use of these agents should be avoided in women who are pregnant or who are breast feeding their children. Cardiac conduction abnormalities (first-degree A-V block) and symptomatic bradycardia are relative contraindications to the use of these medications. Concurrent administration of agents that inhibit hepatic metabolism via CYP450, 3A4, and 2D6 enzymatic pathways (e.g., ketoconazole and quinidine) may increase blood levels of donepezil. Inducers of hepatic metabolism (phenobarbital, phenytoin, carbamazepine, dexamethasone, rifampin) may decrease donepezil blood levels. To-date, there are no reports suggesting that the use of these agents in persons with traumatic brain injury is associated with a change (positive or negative) in seizure frequency.

### **CDP-Choline**

Cytidine 5'-diphosphocholine (CDP-choline or citicoline) is an essential intermediate in the biosynthetic pathway of phospholipids incorporated into cell membranes. Orally ingested CDP-choline is metabolized into its two principal components, cytidine and choline. CDP-choline appears to activate the biosynthesis of structural phospholipids in neuronal membranes, increase cerebral metabolism, and enhance activity of dopamine, norepinephrine, and acetylcholine (157, 233). In light of these



properties, CDP-choline might be expected to improve posttraumatic cognitive impairments.

Calatayud et al. (1991) (234) performed a single-blind randomized study of 216 patients with severe or moderate TBI during the acute post-injury period. They observed improvements in motor, cognitive, and psychiatric function during treatment with CDP-choline, and use of this agent was associated with decreased length of stay in the hospital. Levin (1991) (235) performed a double blind placebo-controlled study of 14 patients to evaluate the efficacy of CDP-choline for treating post-concussional symptoms in the first month after mild to moderate TBI. Oral CDP-choline (1 g daily) and placebo control groups were matched for age, education and severity of initial injury (as assessed by impairment of consciousness). CDP-choline reduced the severity of post-concussional symptoms and improved recognition memory for designs. Other aspects of neuropsychological performance were not significantly influenced by this treatment.

CDP-choline is available in the United States only as an over-the-counter nutritional supplement, and is most commonly formulated in 250 mg capsules. The content and purity of CDP-choline formulations may vary considerably, both within and between manufacturers. Patients electing to undertake treatment with CDP-choline should be cautioned about these problems and monitored carefully for both beneficial and adverse reactions during its use. A metaanalysis of studies using CDP-choline in elderly patients suggests that its use is associated with fewer adverse effects than placebo (236), and there are no reports of serious adverse events related to treatment with this agent among persons with TBI. At present, the limited scope of the relevant literature and the lack of rigorous FDA scrutiny of the safety, tolerability, and efficacy of this agent preclude recommending routine use of CDP-choline in this population. However, for patients unwilling or unable to take other prescribed medications, CDP-choline may be a "nutritional supplement" that some patients may find acceptable and of modest benefit.

## SUMMARY

Pharmacotherapy is one of several potentially useful strategies for the treatment of posttraumatic cognitive impairments. Prior to initiating any such treatment, following the basic principles of pharmacotherapy is imperative. Other neuropsychiatric conditions and other ongoing treatments should be evaluated in order to determine whether such may be contributing to an individual's apparent cognitive problems. The use of agents that are known to interfere with cognition in this population, including typical antipsychotics, anticonvulsants, and benzodiazepines, should be discontinued where possible.

If treatment with such medications is needed, those least likely to impair cognition should be used whenever possible. When pharmacotherapy of posttraumatic cognitive impairments is considered, the period over which an empiric trial of such medications will be undertaken should be defined prior to starting treatment. Specific target symptoms should be defined, and assessment of cognition using standardized bedside or formal neuropsychological measures before and during treatment should be performed. When treatment is initiated, using a start-low, go-slow approach that includes careful monitoring of adverse and drug-drug effects is recommended.

Our present understanding of the neurochemistry of cognition and the neurochemical consequences of TBI suggest that catecholaminergic and cholinergic function are likely to be the most useful neurochemical targets for pharmacologic intervention among persons with typical posttraumatic cognitive impairments such as hypoarousal, inattention, slowed processing speed, memory impairments, language disturbances, and executive dysfunction. It is possible that as more effective and tolerable NMDA receptor antagonists are developed, glutamatergic dysfunction in the acute, post-acute, and late post-injury periods may become a reasonable target for pharmacologic intervention as well.

Although there is less evidence of persistent catecholaminergic deficits among persons with TBI as a group, interindividual differences in the integrity of cerebral catecholaminergic systems post-injury and/or the metabolism of catecholamine neurotransmitters may offer some explanation for the apparent cognitive benefits afforded by catecholaminergically-active agents in this population. Although there is better evidence for persistent cerebral cholinergic dysfunction in association with cognitive impairments following TBI, the number of studies investigating cholinergic augmentation strategies and the strength of the evidence they provide are at present limited. Consequently, only preliminary treatment recommendations regarding the use of medications that increase cerebral cholinergic function can be offered.

In general, patients whose most troubling cognitive impairments include arousal, impaired speed of processing, and inattention may benefit from treatment with a psychostimulant such as methylphenidate. These agents may also improve posttraumatic language, praxis, and executive function impairments, and most of these agents appear to modestly improve some neurobehavioral functions such as apathy, agitation, and perseveration. The present evidence suggests that methylphenidate should be regarded as first-line therapy when an agent from this medication class is used. If methylphenidate proves ineffective or produces intolerable side effects, dextroamphetamine, amantadine, or bromocriptine may be useful alternative stimulant medications. In cases where none of these are effective, clinicians might consider use of

modafanil, carbidopa/L-dopa, or other non-standard agents with stimulating properties such as protryptline or lamotrigine.

Use of psychostimulants in the acute rehabilitation setting may facilitate engagement in rehabilitation therapies, and it is possible that such treatment may hasten the recovery process (functionally, if not also neurobiologically). If used during the post-acute injury period (during which spontaneous recovery may occur), periodically decreasing the dose of these agents after maximal cognitive benefit has been achieved is recommended in order to determine if continued prescription of a psychostimulant is still necessary. When used in the late post-injury period, common clinical experience suggests that these medications maintain their effectiveness over the long-term and that abuse of and/or dependence on these agents is rare.

Among patients whose principal posttraumatic cognitive impairment is in the domain of memory (encoding, retrieval, or both), cholinesterase inhibitors may be of some benefit. Cholinergic augmentation would be predicted to have additional benefits on posttraumatic impairments in arousal, attention, language, executive function, and frontally-mediated behaviors, but the evidence in support of this prediction is at present preliminary. Among the cholinesterase inhibitors, donepezil is used most commonly and is for the present the agent with the most published evidence with which to support and guide its use. When patients respond to treatment with this agent, these benefits appear to be sustained during continued treatment over relatively long periods of time (i.e., months to years). It is not clear whether the other commonly used cholinesterase inhibitors (i.e., rivastigmine, galantamine) afford similar benefits, but there are theoretical reasons to expect comparable effects during treatment with these agents. Although the majority of reports describing the use of cholinesterase inhibitors in this population focus on the treatment of persons in the late post-injury period, these agents may be of use in the acute rehabilitation setting as well (237). If used during the period in which spontaneous recovery is likely to occur, periodic dose reduction and/or discontinuation of these agents is prudent in order to determine whether their use is still needed. In our experience, cognitive impairments that emerge following such dose reductions and/or medication discontinuations remain responsive to treatment once it is reinstated.

In the absence of cost-effective and widely available *in vivo* markers of neurotransmitter function with which to guide the selection of a class of medication, pharmacologic treatment of posttraumatic cognitive impairments in an individual patient remains a matter of clinical judgment and empiric trial. Some patients respond robustly to catecholaminergic agents, others to cholinesterase inhibitors, some require treatment with some combination of these

agents, and others respond poorly to all presently available medications. Additional studies are needed to clarify which agents are most effective for which types of post-traumatic cognitive impairments and better methods are needed to facilitate the identification of patients most likely to respond to such pharmacotherapies.

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# 54

## Neuropharmacology: A Rehabilitation Perspective

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### INTRODUCTION: REHABILITATION PHILOSOPHY

Traumatic Brain Injury (TBI) is not a homogenous entity. Rather it encompasses a series of mechanisms that may each have a preferential effect on different regions of the brain and/or effect preferentially specific types of neuronal populations (1). One needs to consider the mechanism of TBI whether it is blunt trauma to the outer cortex, diffuse axonal injury (DAI), induced intracerebral hemorrhage (as well as the type of hemorrhage), and complicating factors such as anoxia and secondary ischemia when considering injury, prognosis and treatment (1–4). Consequently, it is unrealistic that one approach will fit persons with TBI. This is likely the case on both a mechanical as well as person specific (gender, genetic) plane. What is most important to stress is that there is no “silver bullet” that will treat each area of the brain and its specific cell types with equal efficacy. TBI and its subsequent recovery are a continuum of events that are spread out over several months or years.

A second principle that has become quite evident is that what may be useful early in TBI will not be useful later in the recovery stage and may be detrimental. The very time course of injury cascades suggests that some mechanisms that enhance injury in the acute period encourage recovery in the post-acute period. This fact leads to some of the clinical controversies that shape the

rehabilitation perspective of neuropharmacology. Furthermore, what may be neuroprotective or enhance recovery of one cell type may not have any effect on another type of neuronal cell population or even may be detrimental to that cell population (1). There is a complex interaction between the various neuronal populations and their associated glial cells that we are only just beginning to understand.

Despite the fact that TBI is the number one cause of disability in the U.S and comprises 12% of all hospital admissions in the United States (5–13). The current state of research funding in TBI has traditionally been abysmal especially for postacute TBI. This fact is compounded by professional perceptions. Thus much opportunity exists to understand the role of rehabilitation neuropharmacology in the recovery process and how pharmacology can interact with recovery programs.

However, there have been some advances in our understanding of the mechanisms of injury and processes that follow in TBI. This has resulted in some general principles that have evolved regarding the mechanism of injury, the location of injury, the cell types involved and the various neurotransmitters that may be affected following TBI. All of this leads one to considerable trepidation when utilizing medications that may affect the neurotransmitter systems of the brain following TBI. This chapter will serve to outline some theoretical principles of rehabilitation neuropharmacology; these principles of



injury and neurotransmitter function will be high lighted by their role in the acute injury and recovery process. We also will focus on the controversy they raise that help to shape the clinician perspective of neuropharmacology. This is not an all-inclusive discussion as it is beyond the scope of a chapter but should aid in the readers' understanding of the various other chapters in this book.

**MEDICATION PRINCIPLES**

**Early vs. Late Effects**

Acute TBI is really a series of mechanical events that effects the physical structure of the brain followed by a series of physiological and biochemical responses. When mechanical energy is applied to a substance it is deformed as defined by its mechanical property interrelations (elastic, viscous, or plastic response). The deformation response is time dependent, and dependent on the amplitude of the impact energy wave. When some of the energy is transmitted from the deformed structure to the structures it contacts, there are forces deforming these structures as well (1). If the elastic limit of a structure, such as the cell membrane, the neural filaments and other intraaxonal organelles, is exceeded then there will be a permanent physical deformation to these

structures (1). These factors are often referred to as the primary injury and reflect clinical process such as contusion, intra and extra axial lesions.

This is followed by a series biochemical of events. After the initial period of injury there is a prolonged progression of secondary events that may ultimately result in neuronal and or glial cell death. Maxwell et al recently summarized this theorized sequence of events (14). After injury, there is a depolarization followed by a focal loss of axonal transport as a result of disruption of the cellular organelles. One of the consequences of DAI is direct intracellular injury from direct mechanical displacement of the cytoskeleton and cytoplasm (15). The cascade of biochemical events that leads to further neuronal cell injury and axonotmesis probably exacerbates cellular injury and death. This injury process may involve the neuron cell body and even the glial cells. The sequence of events involves the depletion of adenosine 5'-triphosphate (ATP), intracellular calcium overload, and the production of strong oxidants resulting in oxidative stress (1, 16). The energy failure mechanism is key to the injury process. Clearly, injury to the mitochondria results in a decrease in the local production of ATP within the cell (17). Without ATP, the ion pumps that maintain Na<sup>+</sup>, K<sup>+</sup> and Ca<sup>++</sup> homeostasis within the axon begin to fail (1, 18) (Figure 54-1).

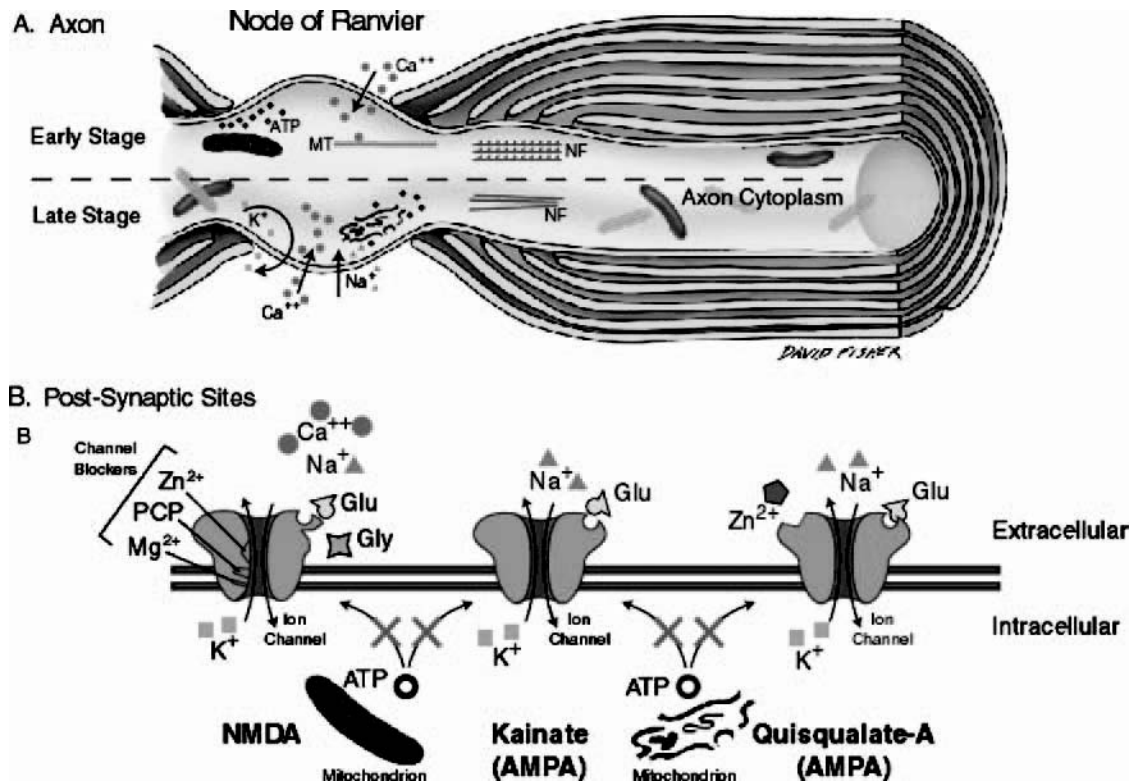


FIGURE 54-1

Axonal injury. (From *Archives of Physical Medicine & Rehabilitation*, V82. Copyright © 2001 American Congress of Rehabilitation Medicine and the American Academy of Physical Medicine and Rehabilitation. Reprinted with permission.)

Neuronal cell death as a result of neuronal and glial cell injury is in part mediated by the secondary release of glutamate activating NMDA channels and alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptors on the neuronal cell body (1, 18, 19). After neuronal cells start to die and their membrane integrity is breached, more glutamate, free radicals and strong oxidants are released and the cycle repeats itself (1, 15). The influx of calcium through voltage-gated calcium channels may cause further cellular death and the release of more glutamate and inflammatory substances resulting in the activation of more n-methyl-d-aspartate (NMDA) receptors (1, 18).

Except for the secondary ischemia and anoxia complications, it appears this whole process is much more prolonged series of events than noted to occur in stroke. Animal and basic science data indicates that hours after acute TBI as much as 50%–60% of the neurons affected could potentially be saved via intervention. This is very different than that noted with ischemic stroke where perhaps only 15% of the neurons might be salvageable after 4 hours or more after the event. This fact raises potential clinical concerns regarding early activation and intervention. The reason is that the penumbra of secondary biochemical affects that can cause cellular death is quite large in trauma versus that noted in ischemic stroke (1). These principles are well established when one compares a stroke due to an intracerebral hemorrhage versus a stroke due to ischemia (1–4).

The trimming of various interventions may be key. As an example of what one uses early may be detrimental later, it is clear that seizure prophylaxis with phenytoin during the first week following injury may help prevent seizures, but that treatment prophylaxis for up to six months may slow recovery (20). It has been suggested that phenytoin may actually be neuroprotective and prevent further damage as it acts as a sodium channel blocker (21). This is the oldest example of a medication that is useful early after injury and is detrimental during the later stages of recovery following TBI. It resulted in the early practice guidelines to originating from the Brain Trauma Foundation and American Academy of PM&R (20, 22).

### Neuroprotective Agents

Recently there has been considerable focus on agents that may block excitatory neurotransmitters that can cause cellular death in already injured and susceptible neurons (23). Drugs that block NMDA channels, AMPA channels as well as the cytokines that are increased after TBI have been the focus of much research (14). Over the first few hours following TBI, there is compaction of the neurofilaments and collapse of their side arms as well as a loss of axonal microtubules (24, 25). The changes in the neurofilaments correspond with an influx of extracellular

calcium resulting from the altered membrane pump Ca-ATPase and ecto-Ca-ATPase activity (25). High levels of calcium also activate several lipases, which results in the production of arachidonic acid leading to inflammatory eicosanoids that promote neutrophil, macrophage invasion and the production of more strong oxidants (26–28). In other words, those cells that have been injured, but have enough metabolic capability to “hold on,” are pushed over the edge to cell death by secondary factors that increase calcium influx into the cell. The cycle repeats itself as the calcium/sodium influx reaches a critical level in the adjacent cells; there is more cellular necrosis and apoptosis (29). The prolonged period of elevated intracellular Ca<sup>++</sup> activates the calcium-dependent neutral cysteine proteases such as caspase-3 and calpains, which hydrolyze proteins resulting in more cellular necrosis and apoptosis (16, 30, 31). The slow progression of neuronal injury may suggest that apoptosis may be occurring with this type of injury due to the oxidative stress that accompanies reduced-glutathione depletion (32).

Secondary biochemical pathways, particularly those focused on the reduction of sodium and calcium influx into neuronal cells following TBI, which eventually activate the apoptotic pathways have also been the focus of considerable scrutiny (1, 2). Glutamate is often mentioned as the mediator of the final common pathway (1–4).

However, it is also clear that glutamate and other excitatory neurotransmitters are required if one is to learn adapt and take advantage of the neuroplasticity that is present in all of our brains (1). Without a release of glutamate we cannot learn. Thus long-term glutamate suppression is not optimal for during the rehabilitation process. The ability to learn as indicated by ones educational level is the most profound predictor of recovery in CNS injury. If we block these pathways with medications we may thus block the recovery process. This may be most important in the first months following TBI. Thus a fundamental controversy is when the injury cascade slows down and the process of recovery begins.

### Enhancing Neuroplasticity

On the other hand it may be just as detrimental to utilize those drugs or treatments that may enhance neuroplasticity too early in the recovery process. This includes medications that enhance excitatory neurotransmitters as well as therapy interventions that may increase these same processes. It has been recently established in animal models that rehabilitative physical or cognitive therapy started too early after neuronal injury may increase damage (33). Furthermore, over stimulating the neuronal process to fatigue may also cause cell death. Understanding this process further has important implications for rehabilitation.

**NEUROTRANSMITTER SYSTEMS**

**Cholinergic System**

As an example let's take a look at the critical cholinergic systems in the brain. The cholinergic system is intimately involved in the pathways associated with memory as well as in patterned motor movements. A lack of cholinergic neurons has been implicated in Alzheimer's disease. Over activity of the cholinergic system with regard to a balanced affect from the dopaminergic system has also been implicated in the development of tardive dyskinesia, and other associated movement disorders (34–36).

The hippocampal pathways have been considerably implicated in the development of antegrade memory loss associated with TBI. This is particularly true of DAI, which may be a factor in over 1/2 of all TBI. Secondly, it is well established that anoxia preferentially affects these areas. This region is rich in cholinergic contribution. Within 10–13 minutes of induced anoxia there is calcium influx into the neurons of the hippocampus and is followed by cellular loss (37). Antegrade posttraumatic amnesia (PTA) is one of the most profound developments of TBI. Preserving and subsequently enhancing these pathways may be of paramount importance.

Acetylcholine receptors are classified as either nicotinic, muscarinic or activate alpha-Latrotoxin. Acetylcholine receptors are ligand-gated cation units composed of several different polypeptide groups (38). The activation of acetylcholine receptors leads to an influx of Na+ and an efflux of K+ thus resulting in cellular depolarization. Naturally occurring or synthetic compounds effect cholinergic neurons either positively or negatively. Muscarinic receptors employ a G-protein activation system while nicotinic receptors do not, there effector mechanism is shown in figure 54-2 (39). Cholinergic neurons can be facilitated by the administration of cholinesterase inhibitors. Cholinesterase inhibitors have also been employed as nerve gases and have a clinical role in the treatment of myasthenia gravis. Several antagonists of acetylcholine receptors exist and may be clinically useful in the acute care period after brain injury. Atropine blocks acetylcholine receptors at muscarinic receptors only while botulinum toxin inhibits the release of acetylcholine (40).

RECEPTOR	G-PROTEIN	EFFECTOR MECHANISM
M1, M3, M5	Gq	↑PLC, ↑ phosphoinositide hydrolysis; ↑IP3; ↑[Ca2+]i
M2, M4	Gi, Go	↓adenylyl cyclase; ↓cAMP; ↓Ca2+ influx/ ↑K + efflux

RECEPTOR	G-PROTEIN	EFFECTOR MECHANISM
α4β2, α7, α3β4	NA	Ligand-gated ion channel; Na+/Ca2+ influx; K+ efflux

*Acute Injury*

In the first week following injury it has been postulated agents that can protect these neurons may be quite useful. Cannabinoids, naturally occurring (marijuana), endogenous or synthetic (dexamabinol) have been theorized to be useful in TBI where this region is susceptible to injury (41). Studies with the synthetic cannabinoid dronaxinabol have improved TBI patient outcomes as measured by the Galveston Orientation and amnesia test (GOAT). However, they did not improve other outcome measures that may be more dependent on other neuronal cell types. A recent multi center trial sponsored by Pharmos was reported a negative for the primary outcome measure (40).

*Recovery*

On the other hand the neuroscience literature is replete with examples of medications and substances that block these cholinergic pathways and accelerate the processes noted with memory loss or inhibit the recovery of memory (42, 43). This needs to be kept in mind when treating patients following TBI. Profound and long-term blockade of the muscarinic system can worsen the Alzheimer's pathology associated with Parkinson's disease (42–44). Furthermore, long-term use of cannabinoids can be detrimental to memory pathways in otherwise healthy individuals (42).

These drugs and substances should be evaluated in the recovering person with TBI. At the very least they likely will impede recovery in a TBI patient. On the other hand donepezil, an acetylcholinesterase inhibitor has been suggested to improve memory disorders following traumatic brain injury (45–48)

*Controversy*

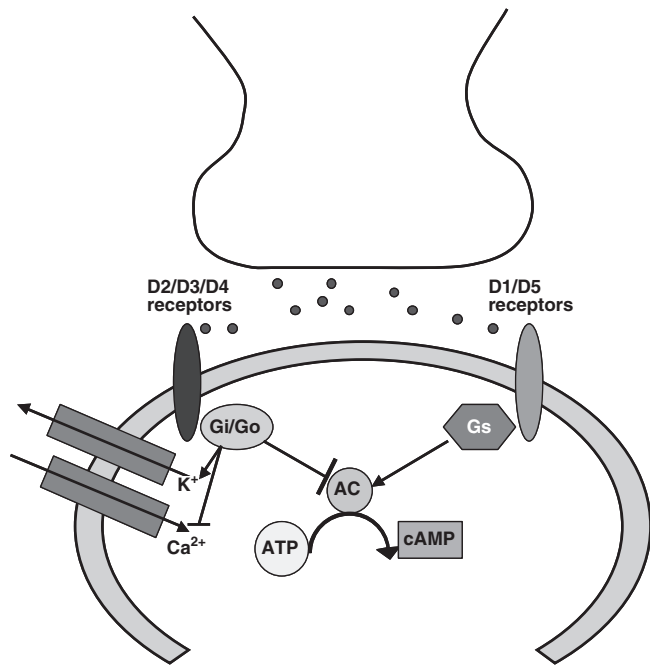
The level of evidence to support the use of cholimemetic agents after TBI is less than robust. The use of citicoline (a phosphosphingolipid) has been preported to have both neuroprotective and neurofacilitatory properties (49, 50). The acetylcholinesterase inhibitors have been studied in a limited fashion in the brain injury population (51, 52). The effects of cholinergic augmentation with donepezil on short-term memory and sustained attention have been

examined in one randomized, double-blind, placebo-controlled trial Zhang studied twenty patients with TBI who were randomized from two postacute rehabilitation clinics; 18 completed the trial. During the donepezil phase, the drug was administered at 5 mg/day for the first two weeks and 10 mg/day for the remaining eight weeks of the trial. Group analysis showed significant benefits of donepezil on neuropsychological functioning (52). Benefits of donepezil were sustained after the washout period. An early case series found that this medication did help in self-reported improvement of memory in two persons with acute TBI, yet this series was problematic in its design and control (48). An open label trial of 10 subjects with TBI treated with donepezil, patients noted a clinical global improvement (46). These agents have not yet been shown to assist in emergence from posttraumatic amnesia.

**Dopamine Pathways**

The dopamine neurons are generally located in the mid-brain the periventricular areas of lateral ventricles including the very well known substantia nigra pathways. The most important dopaminergic pathways are the nigrostriatal, tuberoinfundibular, mesolimbic and mesocortical pathways (53, 54). Dopamine receptors exist as families of receptors with their designation in part being determined by their ability to activate adenylyl cyclase (D1, D2, D3, D4, D5) see figure 54-3 (54). The D1 and D5 family of receptors activate adenylyl cyclase while the D2, 3 and 4 family of receptors inhibit adenylyl cyclase. These receptors all employ G proteins to inhibit or active processes (54). Dopamine is associated with motor movement and probably arousal. The pathways project to the hypothalamus and are associated with autonomic functions and hormonal levels.

In acute injury, a vast excitotoxic cascade occurs. It has been well established the increases in dopamine are correlated with increased cell death in the regions where dopamine acts as a neurotransmitter (55). Furthermore medications that block dopamine release or receptors have been implicated in slowing neuronal recovery (36, 56–58), these agents may affect hormonal levels through their affects on the hippocampal releasing hormones, and cause dysautonomia. Deficits associated with decreased



**FIGURE 54-2**

Dopamine receptor

dopamine such as movement disorders, and neuroleptic malignant syndrome is associated with blockade of the dopamine pathways as well (36).

**Recovery**

Patients who have had profound disruption of the dopamine pathways as noted in DAI and anoxic injury may forever be very susceptible to the side effects of medications that block the D1-D5 pathways (35, 36). For this reason these medications need to be judiciously utilized with preference to medications that block as few of these pathways as possible. For this reason medications that block the dopamine pathways are generally restricted in the early recovery stages of TBI due to their potential clinical effect.

**Controversy**

Typical antipsychotics and atypical antipsychotics carry varying degrees of dopamine blockade. Typical antipsychotics exist along a spectrum carrying various degrees of dopamine blockade (mostly D2) and anticholinergic activity (59). Atypical antipsychotics have activity not only via dopamine blockade but also on the serotonin system (59).

Typical antipsychotics have been used for the immediate control of aggression or agitation in TBI (60). These agents have the potential concern of lowered seizure threshold and clouded sensorium. As with other patient groups, neuroleptic malignant syndrome has been reported

**TABLE 54-3**  
**Dopamine**

RECEPTOR	G-PROTEIN	EFFECTOR MECHANISM
D1, D5	Gs	↑adenylyl cyclase; ↑cAMP
D2, D3, D4	Gi, Go	↓adenylyl cyclase; ↓cAMP; Ca <sup>2+</sup> /K <sup>+</sup> channels

with the administration of typical and atypical antipsychotic agents. Presenting symptoms can include fever, leukocytosis, and muscle stiffness; this entity carries a potential mortality of 10% (61). The source of these adverse events appears to be the typical antipsychotic medications particular affinity for the D2 dopamine receptor. Atypical antipsychotic agents have less D2 activity and more 5HT<sub>2a</sub> activating thus theoretically reducing some of the undesirable effects and adrenergic blockade (59). Recently clinical concerns with cardiac dysfunction have been raised in the dementia population with the use of atypical and typical antipsychotic agents (62).

While numerous studies have been done in animal models there is a lack of clarity in optimal timing and in human data. Animal models of recovery after TBI consistently demonstrate a negative impact of dopamine blockers on recovery in the postacute period (57, 63). Yet not all animal models are clear on this issue. In an animal study evaluating the effects of antipsychotics on cognitive function after TBI, haloperidol was demonstrated to be harmful while olanzapine was not (64). Recent work has demonstrated a negative impact of chronic risperidone use (65). Perhaps these differences are explained by the relatively strong D2 receptor activity of risperidone (65).

While most rehabilitation clinicians treating those with TBI would attempt to avoid dopamine blockade the actual human evidence for this is rather weak. Rao et al studied the impact of haloperidol in a rehabilitation setting and noted no change in outcome but a longer length of posttraumatic amnesia in the haloperidol group (66). Maryinak et al demonstrated the successful use of the older antipsychotic methotrimeprazine in persons with TBI admitted to a rehabilitation unit (67). These authors noted that while those treated with the antipsychotic had a longer length of posttraumatic amnesia is likely reflected a greater injury severity (67). Other authors have noted that weaning antipsychotics in the chronic setting results in improved neuropsychological test scores (68). Of interest however is a recent study suggesting a benefit to the use of haloperidol in the ICU setting. Milbrandt and colleagues examined a total of 989 persons with ICU stays and mechanical ventilation of greater than 48 hours (69). Haloperidol use was associated with lower hospital mortality. While this retrospective study has limitations, this data appeared to remain consistent for those with trauma and neurological dysfunction. The authors postulated that at least acutely haloperidol inhibits the secretion of proinflammatory cytokines.

Medications that may increase dopamine have been postulated to enhance recovery from TBI (70, 71). The most studied of these medications is amantadine, which also may have effects on various neuronal growth factors. Other medications such as bromocriptine that demonstrate specific D1-D2 receptor pathway activity have also been useful (71).

The disruption of the dopaminergic pathways has also been implicated in the development of psychiatric disorders following TBI (35, 36). Delusions, hallucinations, and various behavioral dyscontrol syndromes have been implicated with TBI.

The role of dopamine enhancing medications in the potential recovery of persons with TBI remains an issue of great interest. These agents have been employed for aphasia, hemineglect, arousal, agitation and dysautonomic syndromes. Dixon and Klein have demonstrated the role of amantadine in the treatment of a laboratory model of chronic TBI (72). Bromocriptine has also been shown to improve lipid peroxidation after TBI (73). Other agents such as selegiline have shown promise in the laboratory (74). Clearly, clinical trials are lacking and little level I evidence exists to guide clinicians in the use of these medications. Potential side effects of these medications include: dyskinesia, hypotension, lowered seizure threshold, hallucinations and behavioral dysfunction.

While many clinicians use neurostimulant medications for the treatment of hypoarousal in persons with TBI, unfortunately the literature to support their use is sparse (40). Amantadine has both pre and post dopaminergic activity as well as functioning as a NMDA antagonist (71). In a case report by Zafonte and colleagues, a male patient in a minimally conscious state regained full consciousness when placed on the dopaminergic agent amantadine but subsequently experienced a significant decline when the medication was withdrawn (76). A double blind placebo cross over study by Meythaler and colleagues, showed significant improvements in DRS scores and FIM-cognitive scores in groups taking amantadine were found, regardless of when it was started (71). Additionally, amantadine has shown promising results when given in the acute phase of TBI. Saniova et al. found decreased mortality rates and improved GCS scores in a small group of persons admitted to an ICU after severe TBI who were given a three-day course of amantadine (77). This agent is presently under evaluation in a multicenter trial to evaluate its impact on arousal. McDowell tested a group of 24 subjects with TBI using a double blind, placebo-controlled crossover trial (78). Bromocriptine was found to improve performance on some tasks served by prefrontal function, but not others. Dobkin had previously shown improvement in antegrade amnesia in a women with TBI (79). Substantial work still remains to identify the specific syndromes and characteristics of persons who respond to these medications.

### Serotonergic Pathways

The serotonin pathways are found predominately in the midbrain and brain stem but are distributed diffusely throughout the CNS. They have profound projections throughout the brain including to the frontal lobes and

the hippocampus (80, 81). It has been theorized that these pathways are most disrupted by DAI. Serotonin (5-hydroxytryptamine or 5-HT) is likely the most phylogenetically ancient of currently known neurotransmitter molecules. Serotonergic neuronal cell bodies are organized in two distinct groups (81); caudal (in the medulla oblongata and the caudal half of the pons) and rostral (in the midbrain and rostral pons) (81). The rostral 5-HT neuron axons ascend toward the forebrain, while those from the caudal group descend to brainstem structures and the spinal cord. Numerous serotonin receptor types have been identified (82, 83) (Figure 54-4). The current classification system takes into account drug related properties, as well as information about amino acid sequencing of the receptor. It is the receptor interaction with the G protein that permits the particular receptor to modulate the activity of different effector systems such as ion channels, substances like adenylyl cyclase. The 5HT1 family and 5HT2 family represent the major classes of serotonin receptors this family also includes the 5HT4, 5HT6 and 5HT7 all of whom are G protein dependent (83, 84). The 5HT3 receptor system is a gated ion channel dependent system and represents a separate functional family of receptors. These receptor differences create opportunity and hazards in drug development and clinical utility.

These widely distributed serotonergic pathways are involved in diverse cognitive functions. Data suggest that serotonergic neurotransmission plays a major role in stabilizing and modulating brain function (84, 85). The rostral part of the serotonergic raphe system consists of the caudal linear nucleus (in the midbrain), the dorsal raphe nucleus (extending from the caudal midbrain to rostral pontine levels), and the median raphe nucleus (superior central raphe nucleus found in the rostral pons) (80, 81). In the caudal division there are descending serotonergic neuronal projections found in the raphe magnus nucleus, raphe pallidus nucleus, and raphe obscurus nucleus. In addition there are serotonergic neuronal cell bodies present in the medullary reticular formation (involved in alertness and wakefulness) and other non-raphe regions such as the hippocampus (involved in memory functions) and the substantia nigra (involved with motor control) (80, 81) (see table 54-4).

### Acute Injury

Very little work has been performed on the affects of acute serotonin disruption following TBI. However, increasing the levels in the first week following injury is hypothesized to have the same affect of causing increased neuronal cell death as with other excitatory neurotransmitters.

Unfortunately, projections of the serotonin system, including to the forebrain, limbic areas, and hippocampus,

**TABLE 54-4**  
**Serotonin**

RECEPTOR	G-PROTEIN	EFFECTOR MECHANISM
5-HT1A,1B, 1D, 1E, 1F	Gi, Go	↓adenylyl cyclase; ↓cAMP; ↓Ca <sup>2+</sup> influx/↑K <sup>+</sup> efflux
5-HT2A, 2B, 2C	Gq, G1	↑PLC, ↑ phosphoinositide hydrolysis; ↑IP <sub>3</sub> ; ↑[Ca <sup>2+</sup> ] <sub>i</sub>
5-HT3	NA	Ligand-gated ion chan- nel; Na <sup>+</sup> /Ca <sup>2+</sup> influx; K <sup>+</sup> efflux
5-HT4, 6, 7	Gs	↑adenylyl cyclase; ↑cAMP
5-HT5	Unknown	Poorly Characterized

are prime sites of direct or secondary injury resulting from TBI. There is ample evidence that TBI impacts levels of serotonin in the central nervous system (CNS), but whether there is an elevation or depletion of serotonin is a matter of some debate. Several studies have documented elevations of serotonin in the CNS during the hours immediately after CNS injury, possibly extending for several days (85–88). Markianos, et al. found a significant negative correlation between CNS level of serotonin and the Glasgow Coma Scale score obtained at the time of assay, as well as an association of high serotonin levels with subsequent death (89). Under these conditions, serotonin has been suspected of worsening edema and contributing to vascular spasm (85–88). On the other hand, there are also studies that indicate diminished CNS serotonin levels within the first 24 hours after TBI (88–91), even in cases of mild injury (92). The decrease in serotonin level has been documented up to 60 days following TBI (60), suggesting a chronic down-regulation of the serotonergic system. In addition, there is evidence that serotonin may assist in controlling edema and serotonin receptor agonists may diminish the excitotoxic effects of glutamate release, or secondary inflammatory factors after neurotrauma (93, 94). Disruption of normal serotonin functioning has been documented on a chronic basis after even milder injury, based on a diminished prolactin response to buspirone, which activates serotonin receptors under normal conditions and results in prolactin release (90). Animal models also suggest that neuronal synthesis of serotonin may be inhibited even though extracellular levels of the substance may be high (95).

### Recovery

Damaged serotonergic neurons can survive an injury and in time re-energize target regions, reestablishing

synaptic and neurotransmitter function and restoring behavior (1, 95–97). Mature adult neural circuitry can be remodeled and affected by the use of neurotrophic or neurotoxic factors (96). Serotonin facilitation may be involved in controlled neurogenesis. Pharmacological manipulation of neurotransmitter levels, including serotonin, may aid in the repair and reestablishment of useful neural pathways. Serotonin also plays a key role in sleep initiation.

### *Controversy*

Animal data has suggested that 5HT agonist medications may be both helpful and harmful. Repinotan hydrochloride (repinotan) is a highly potent and selective 5-HT(1A) full receptor agonist. This agent has shown rapid uptake and a broad spectrum of neuroprotection in stroke and TBI (97). Kline has reported that 5-HT1A-receptor agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) attenuated traumatic brain injury (TBI)-induced cognitive deficits and histopathology (96). However Wilson studied the selective serotonin 5HT1a receptor agent fluoxetine that in a chronic administration did not impact motor or cognitive recovery (98). Boyeson's team observed that high doses of the phenylpiperazine agents trazodone induced deficits in an animal model of TBI (99, 100).

Thus, there may be a period of time when introduction of serotonin agonist agents might be beneficial to recovery of the normal serotonin response. Selective serotonin reuptake inhibitors are among the most utilized medications in North America. These agents have been employed to enhance arousal, improve behavior, and treat depression and emotional lability. An initial phase I study (101) examining the potential beneficial impact of serotonin agonists on recovery after TBI indicated that sertraline was safe, although the study may have been limited by a small subject pool and a short duration of treatment with an SSRI (2 weeks).

It has been theorized that disruption of these pathways is one of the causes of increased depression following TBI (102, 103). A single blind placebo run in trial by Fann et al demonstrated the potential utility of the SSRI Zoloft in the treatment of depression following mild TBI. These pathways have also been implicated in the development of the emotional lability and emotional incontinence noted to follow TBI (102). The use of SSRI antidepressants has become common during the rehabilitation phase following brain injury due to either stroke or TBI. In two studies, antidepressants were shown to aid in the management of behavioral disturbance. Kant and colleagues gave sertraline for eight weeks to 13 patients with TBI, resulting in decreased outbursts and irritability yet this study failed to clarify this issue (104). Bupropion was reported to

improve psychomotor agitation and participation in therapies in a 20-year-old woman with TBI who had failed treatment with several other medications (105).

Trazodone, a triazolopyridine antidepressant, is a selective 5-HT reuptake inhibitor and 5-HT<sub>2</sub> receptor antagonist and has been frequently used for its sedating effects. Used as an antidepressant, doses of up to 500mg/d are commonly required, however, at lower doses its sedative properties likely result from its antagonistic effect of the 5-HT<sub>2</sub> receptors (106, 107). The effects of trazodone on sleep have been shown to occur after the first dose (107, 108). It has been found to closely mimic the natural sleep cycle by increasing the amount of total sleep, increasing the percentage of deep sleep (stages 3 and 4) and decreasing the number of intermittent awakenings (106, 108–114). Trazodone in one dose of 50 to 100 mg nightly to patients showed improvements in early sleep waking, lack of sound sleep, and difficulty in initiating sleep at two weeks and six weeks with significant increases in total sleep time (111).

Mirtazapine is an alpha<sub>2</sub>-adrenoceptor antagonist as well as an indirect 5-HT agonist, increasing both synaptic norepinephrine and serotonin. Mirtazapine has been found to improve sleep continuity and increase latency to REM sleep, which may in part be due to its antihistamine properties (115). Yet concern exists regarding rapid weight gain have been noted. Further studies evaluating the role of mirtazapine in sleep disorders in the TBI population are warranted in order to evaluate potential cognitive sequelae.

These studies need to be expanded upon and several are underway at the current time. Whether increases in serotonin will improve the functional status following TBI, beyond that associated with affective disorders is not well understood. Just as important is a clearer understanding of the risks of these agents and their effectiveness in this population.

### **Norepinephrine Pathways**

The excitatory norepinephrine pathways are widely distributed in the brain. However, they are most predominant in the neocortex. From a small cluster of neurons in the locus coeruleus axons are projected to vast areas diffusely throughout the central nervous system including the spinal cord, cerebellum, thalamus and cerebral cortex (116). These pathways have profound effects on behavior, affect, motor function and attention to name just a few of the wide effects of NE. As an example of the critical interactions between neurotransmitters a reduction of NE in the frontal cortex has been associated with attention deficits related to new learning (117). Hence, memory deficits may be related to reduced attention without deficits in the acetylcholine pathways.

**TABEL 54-5**  
**Norepinephrine**

RECEPTOR	G-PROTEIN	EFFECTOR MECHANISM
$\alpha$ 1A, $\alpha$ 1B, $\alpha$ 1D	Gq	$\uparrow$ PLC, $\uparrow$ phosphoinositide hydrolysis; $\uparrow$ IP3; $\uparrow$ [Ca <sup>2+</sup> ] <sub>i</sub>
$\alpha$ 2A, $\alpha$ 2B, $\alpha$ 2C	Gi, Go	$\downarrow$ adenylyl cyclase; $\downarrow$ cAMP; $\downarrow$ Ca <sup>2+</sup> influx/ $\uparrow$ K <sup>+</sup> efflux
$\beta$ 1, $\beta$ 2, $\beta$ 3	Gs	$\uparrow$ adenylyl cyclase; $\uparrow$ cAMP

### Acute Injury

Increases of NE are discouraged in the first minutes, hours and days following TBI as the increase alone has been linked to increased neuronal cell death (118, 119). These increases play into the secondary injury cascade and appear to exacerbate other pathways. Indeed, blockade of some NE adrenergic pathways has been hypothesized to be useful in the first few days after injury (120–122).

### Recovery

Long term reductions have been associated with an acquired attention deficit syndrome in TBI. This chronic decrement in response has been demonstrated in animal models (123, 124). Consequently, there has been research on the use of agents to increase NE in the weeks following TBI (125, 126).

### Controversy

D-amphetamine enhances NE release and has been demonstrated to show benefits in dorsal frontal injury. Kline has demonstrated that chronic methylphenidate treatment enhances water maze performance in animal models of TBI (124).

The most commonly utilized medication is methylphenidate (125–127). Methylphenidate is believed to impact its action at least in part by activity at the dopamine transporter (DAT)(128). One group of investigators has conducted two randomized, double blind, placebo-controlled trials using crossover designs to evaluate the effects of methylphenidate on various aspects of attention after TBI (125). Methylphenidate's potential utility was demonstrated in a study of 34 adults with TBI and persistent deficits in attention (125). Significant benefits of methylphenidate were seen on speed of information processing, but not on divided attention, sustained attention or susceptibility to distraction. This well-designed study suggests the potential beneficial effects of methylphenidate on specific aspects of attention after TBI. While it's

role in arousing patients is not clear methylphenidate does appear to improve attention and processing speed. In a study of ICU persons with TBI, early use of methylphenidate was associated with reductions in ICU and hospital length of stay by 23% in severely TBI patients (128). Although concerns in using early methylphenidate therapy exist such as: increasing the excitability cascade and the proper timing of such therapies. Medications indicated for attention deficit, both on label and off label, have been frequently utilized in TBI patients to improve attention and processing speed in those patients with documented deficits. Since attention is related to so many neurocognitive function, there is a significant need to perform further research in this area. Further evaluation of the population specific benefits is also needed.

### GABA Pathways

$\gamma$ -Aminobutyric acid (GABA) is among the most prevalent neurotransmitter in the CNS. It invariably acts as an inhibitory pathway on excitatory neurotransmitters such as acetylcholine, dopamine, glutamate and norepinephrine. GABA pathways are distributed throughout the brain (116, 129).

GABA receptors have been classified into subtypes A, B and more recently C. The GABA<sub>A</sub> receptor is the best understood and has three distinct subunits (116, 129, 130). GABA has been implicated in the inhibition of dopamine, norepinephrine, and cholinergic pathways in the brain. It also modulates the excitotoxicity of Glutamate (116). More recently, GABA has been implicated in the release of serotonin (131). As such GABA is the most widespread neurotransmitter and is invariably inhibitory (116).

### Acute Injury

Because of GABA's effects via the G1 protein at Glutamate activated channels it has been considered to be a potentially neuroprotective agent in the first minutes, hours and days following TBI (116). Unfortunately, GABA is completely hydrophilic and does not cross membranes. This leads us to consider medications that indirectly increase its release.

**TABEL 54-6**  
 **$\gamma$ -Aminobutyric acid (GABA)**

RECEPTOR	G-PROTEIN	EFFECTOR MECHANISM
GABA <sub>A</sub> GABA <sub>C</sub>	NA	Cl <sup>-</sup> channel
GABA <sub>B</sub>	Gi, Go	$\downarrow$ adenylyl cyclase; $\downarrow$ cAMP; $\downarrow$ Ca <sup>2+</sup> influx/ $\uparrow$ K <sup>+</sup> efflux



One potential mechanism linked to the neuroprotective effects acute ETOH exposure following CNS injury is the blocking effects at Glutamate activated NMDA channels (132). However, chronic use of ETOH may actually down regulate the receptors thereby reducing the brain's ability to self protect itself from excitatory neurotransmitters (133–137).

### Recovery

Use of GABA agonists has been implicated to reduce the rate of recovery following brain injury (138). This includes medications such as benzodiazepines and baclofen (139). The benzodiazepines are termed sedative hypnotics, they make you forget and/or they put you to sleep (138, 139). Both conditions are not conducive to recovery. It is felt that the first six months after injury from TBI are most critical to recovery. This means that these medications, often utilized for seizure prophylaxis, spasticity management and behavioral control should be restricted as much as possible.

### Controversy

Benzodiazepines, antiepileptic medications (AED's) and antispasticity agents act via GABA yet their longterm impact of these agents is not well understood (138). Benzodiazepines are the oldest family of medications used for spasticity. Diazepam, the most commonly used agent, acts near the GABA<sub>A</sub> receptor to hyperpolarize the cellular membrane, and thus increases presynaptic inhibition (140, 141). Work on the use of diazepam in spinal cord injury, cerebral palsy and multiple sclerosis demonstrated its efficacy in the treatment of spasticity over placebo (142–143). Diazepam has not shown functional improvement. Diazepam's major limitation is in its rather significant side effect profile is sedation it has limited tolerance of diazepam and thus limit its use in the TBI population (138, 140). Baclofen is active at the GABA b receptor both pre and postsynaptically. It has been employed for the treatment of spasticity in persons with SCI, cerebral palsy, multiple sclerosis, stroke and brain injury (138). Enteral baclofen therapy may be warranted for those with severe spasticity of cerebral origin who cannot tolerate dantrolene sodium and face the risk of severe contracture or loss of range of motion (140).

Baclofen has been noted to produce sedation, especially among those with cerebral disorders. Concerns with the use of this medication include: asthenia, depression, hallucinations, nausea, dizziness and paresthesias. Attention and memory induced deficits have been raised in animal models and observed with humans. GABA facilitatory agents may impair recovery (145). Memory dysfunction has been associated with baclofen therapy in both animals and humans (145, 146). Additional concerns with

baclofen include lowered seizure threshold, and withdrawal syndrome (146). Rapid withdrawal from baclofen therapy should be avoided and can induce seizures, altered mental status, hallucinations, hyperthermia and rigidity (138). Therefore concerns are raised regarding potential negative impact on neurorecovery. One implication of this concept is the long-term use of AED's, particularly those that may function via GABA, are discouraged in the long-term prophylaxis of seizures following TBI. There is considerable evidence they may impede recovery. Finally, inhibiting the effects of excitatory neurotransmitters such as glutamate via GABA invariably affects our ability to learn and adapt. Glutamate is necessary for neuroplasticity and learning and blockade invariably has the potential to reduce the rate and end-point of recovery. The timing of dosing of GABA agonists (early may be better than late) and amount of blockade by the various drugs may be critical.

### CONCLUSION

While this is a brief discussion regarding some of the principles of neuropharmacology following TBI, there is much more to follow in the later chapters of the book. The primary purpose of this chapter is to give one a general outline of some of the major neurotransmitter systems that may affect the outcome from TBI. What has not been explored are therapeutic thresholds and toxicity levels for medications.

More research needs to be performed on the use of medications that modulate transmitter systems and the pharmacogenetics involved in treating such persons. When utilizing medications, thought should be given to their profound effects, often beyond the intended results. Randomized placebo controlled trials are needed to further define the potential benefits and risks of such therapy. In addition, a broad understanding of the "window of opportunity" for such medications is needed. As one reads further chapters in the textbook consider the untoward side effects presented as well as the beneficial uses of medications that may affect the CNS.

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# 55

## Nutraceuticals

*Jeffrey S. Hecht*

**I**n surveys of various patient populations, it has been found that nutritional supplements not prescribed by (or known to) the attending physician are being used (1). Increasingly, physicians are being urged to ask about use of these non-traditional medications and become aware of the common and uncommon interactions with prescribed drugs. A huge and growing business exists for those purveyors of “health foods” and “health supplements”—with large sections of traditional pharmacies carrying them. The German government has long established a bureau to assure standard doses of these supplements, but the US has no such regulation at the present. However, in recent years the federal government, through the National Institute of Health, has established the National Center for Complementary and Alternative Medicine (NCCAM). The NCCAM has sponsored trials with nutritional supplements for dementia, but so far not in the area of traumatic brain injury.

The growing interest in nutritional supplements has led to a growth of research in this area (2), a 1997 survey estimated that 12.1 percent of adults in the United States had used an herbal medicine in the previous 12 months (as compared with 2.5 percent in 1990), resulting in out-of-pocket payments of \$5.1 billion, but little is specifically in the area of traumatic brain injury. Yet, some of the studies are relevant to problems experienced by the brain injured. These include the psychostimulants ginkgo and ephedra,

and the antidepressant St John’s Wort (1, 3). One literature survey of particular value is that by Fugh-Berman and Cott in *Psychosomatic Medicine* (4).

### **NUTRITIONAL SUPPLEMENTS USED TO IMPROVE COGNITION**

*Choline* Choline is an important component of the neurotransmitter acetylcholine. There is evidence that high doses of choline may improve memory in adults. (Doses up to 2500 mg po bid are used.) Choline is one of the B complex vitamins, and occurs in foods such as eggs, meat, fish, nuts, legumes, and soy.

*Phosphatidylcholine* Phosphatidylcholine is the most active ingredient found in soy lecithin. Every cell membrane in the body requires phosphatidylcholine (PC). Nerve and brain cells in particular need large quantities of PC for repair and maintenance. PC also aids in the metabolism of fats, regulates blood cholesterol, and is a component of myelin. PC is a major source of the neurotransmitter acetylcholine. Most of the choline normally present in our diet is in the form of lecithin where it occurs in seed oils and in unrefined foods containing oil.

Supplemental PC increases the amount of acetylcholine available for memory and thought processes. Increasing acetylcholine levels has been shown to improve

performance by humans in a variety of intelligence and memory tests. Acetylcholine also is extremely important in maintaining brain cell structure.

**CDP-Choline, Citidine, Citicoline, cytidine-5-diphosphate-choline, tidinediphosphocholine, Somazina, cytidine 5'-diphosphate choline**

A medication that has been studied over 25 years with demonstrated efficacy in a variety of conditions including traumatic brain injury (TBI) is CDP-Choline. The drug is made of cytidine and choline moieties connected by a pyrophosphate bridge. Cytidine is incorporated into nucleic acids while choline ultimately "is in part converted into betaine, which in turn acts as methyl donor to homocysteine, yielding [14C]methionine, subsequently incorporated into proteins" (5).

Studies in animal models first suggested possible benefit of this drug. One study suggested inhibition of phospholipid breakdown by inhibition of an enzyme that is released following brain injury—phospholipase A2 (6).

Another study noted the strong polar nature of this drug, which prevents it from effectively crossing the blood-brain barrier (BBB). They studied a way to better cross the BBB by trapping citicoline in liposomes with the goal of improving its therapeutic effectiveness. The real therapeutic effectiveness of these citicoline liposome formulations was evaluated by biological assay with levels compared to the survival rate of ischemic reperfused male Wistar rats. Conjugated diene levels in the rat brains were measured, since this is an index of lipid peroxidation in rat cerebral cortex during post-ischemic reperfusion. The best mixture produced a reduction in diene levels of 60% and an increase in rat survival rate of about 24% and compared to the free drug (7). Other studies indicated that CDP-choline decreases edema formation and blood-brain barrier disruption following traumatic brain injury (TBI). One study of controlled cortical impact (CCI)-induced TBI in adult Wistar rats involved administration of the drug immediately post injury and once 6 hours post injury. The animals were sacrificed and the number of hippocampal neurons counted on the seventh post injury day. Treatment with CDP-choline significantly prevented TBI-induced neuronal loss in the hippocampus, decreased cortical contusion volume, and improved neurological recovery (8).

In another study, the authors examined the effect of CDP-Choline on brain edema and breakdown of the blood-brain barrier after TBI. Like the prior study, TBI was created using a CCI device. Half of the Sprague-Dawley rats received intraperitoneal injections of CDP-Choline twice following TBI. No significant benefit was noted at a low dose, but the higher doses (100 and 400 mg/kg) significantly decreased brain edema and BBB breakdown. Neuroprotective effects were demonstrated in the hippocampus as well as the directly injured cortex (9).

A Turkish study demonstrated significant neuroprotective effect of the drug and mortality reduction in rats following experimental cerebral ischemia (10).

A study from the department of neurosurgery at the University of Pittsburgh explored the role of CDP-choline in attenuating deficits in posttraumatic motor and spatial memory performance caused by direct trauma using a CCI model. They also explored whether CDP-choline increases acetylcholine (ACh) release in the dorsal hippocampus and neocortex.

The drug was first administered one day post injury and continued for 18 days. In the behavioral study, traumatic brain injury (TBI) was produced by lateral controlled cortical impact (2-mm deformation/6 m/sec) and administered CDP-choline (100 mg/kg) or saline daily for 18 days beginning 1-day post injury. Between 14–18 days post injury, CDP-choline-treated rats had significantly less cognitive (Morris water maze performance) deficits than injured saline-treated rats. CDP-choline treatment also attenuated the TBI-induced increased sensitivity to the memory-disrupting effects of scopolamine, a muscarinic antagonist. Microdialysis studies demonstrated a significant increase in extracellular levels of ACh in the dorsal hippocampus and neocortex in normal, awake, freely moving rats. The authors opined that this provides additional evidence that spatial memory performance deficits are, at least partially, associated with deficits in central cholinergic neurotransmission and that treatments that enhance ACh release in the chronic phase after TBI may attenuate cholinergic-dependent neurobehavioral deficits (11).

Clinical use of CDP-Choline in neurosurgery was first reported in the Japanese literature (12). Ogashiwa's article first reported both on the whole-body distribution of the drug in Wistar rats. It then went on to describe administration of CDP-choline to seven patients by intrathecal route to bypass the BBB. His second study reported benefit from 39 infusions given to 15 patients (13). Use of the drug in 60 cases of severe head injuries (wide-spread cerebral contusions and/or severe concussion) was reported by Cohadon and others in the French literature. They postulated that a shortening of the comatose period and an acceleration of neurological deficits recovery noted in the treated group was due to reduction of cerebral edema (14).

The authors of a Spanish single blind randomized study of 216 patients with moderate or severe brain injury study found "a trend towards a greater improvement in motor, cognitive and psychic alterations in the patients treated with CDP-choline, as well as a shortening of the stay in the hospital ward in the patients receiving this drug that initially presented with severe head injuries" (15).

By 2001, use of CDP-choline had apparently become part of standard neuro traumatology practice in Japan (16). The authors observed, "There appear to be two obvious differences in selection of pharmacological

therapies among neurosurgeons in Japan and those in other countries; neurosurgeons in Japan prefer glycerol to mannitol for osmotic control of intracranial pressure, and barbiturate to morphine as sedatives. Two drugs are currently available in Japan for promoting the recovery from disturbance of consciousness after head trauma: cytidine diphosphate choline (CDP)-choline (Nicholin, Takeda Chemical Industries, Ltd., Osaka) and protirelin tartrate (Hirtonin; thyrotropin-releasing hormone (TRH) analogue, Takeda). Another TRH analogue, NS-3 (montirelin hydrate), is currently submitted to the Ministry of Health and Welfare for approval.

CDP-Choline has been the subject of double-blind placebo-controlled trials in humans in Japan with another type of brain insult—ischemic stroke—where it was found to be efficacious. Significant improvements in level of consciousness (Tazaki) and hemiplegia (Hazama) were noted in the studies (17, 18). In Spain, it has been reported to be effective in clinical trials of patients with Parkinson's Disease (19, 20) and Alzheimer's disease (21). CDP-Choline has been used late after brain injury as well as in the early stages. Harvey Levin, at the University of Texas in Galveston, reported it to be effective in a double-blind placebo-controlled trial of 14 patients with mild to moderate closed head injury who had postconcussional symptoms persisting for one month (22). Leon-Carrion and others, in Spain, reported that CDP-Choline improved cerebral blood flow of seven patients (by reversing brain injury-induced hypoperfusion) in the inferior left temporo-basal region. Additionally, they noted an improved response to neuropsychological rehabilitation—specifically observing that the domains of “memory, learning processes and verbal fluency . . . improved significantly after treatment” (23). One case report suggesting positive effects on recovery was particularly interesting as it is autobiographical (24).

A review of the use of CDP-choline as well as other cholinomimetic agents is helpful. Their primary observation is that “preliminary data in traumatic brain injury suggest acetylcholine esterase inhibitors may play a significant role in the treatment of this patient population as well.” (25)

Most published studies in animals (26, 27) and humans (28, 29) indicate that CDP-choline is safe. No side effects were observed in the studies on rats and dogs. One of the human tolerance studies of 2817 patients with neurological diseases on the medication for therapeutic reasons observed side effects in 5.01% of the patients: “the most frequently seen were digestive troubles, observed in 3.6% of the cases”. The mean dose in that study was 6 ml/day. The other study of 12 adult healthy volunteers noted, “transient headaches were the only untoward events recorded”, but the frequency was 33% in the “low dose” (600 mg/day) group and 42% in the “high dose” (1000 mg/day) group.

*Ginkgo biloba.* Ginkgo has been used to improve memory and attention. Ginkgo biloba extract is the most commonly prescribed plant remedy in the world. For thousands of years, Ginkgo has been part of the armamentarium of traditional Chinese herbal medicine. In Indian Aryeurvedic medicine, it is part of the elixir called Soma.

Modern studies have also demonstrated the effectiveness of this medication. A randomized, double-blind, placebo-controlled trial of 309 patients with Alzheimer's or multiinfarct dementia concluded that Ginkgo was beneficial in the treatment of dementia (30). The authors concluded that Ginkgo biloba “was safe and appears capable of stabilizing and, in a substantial number of cases, improving the cognitive performance and the social functioning of demented patients for six months to one year.” Benefits were equivalent to Tacrine or Aricept—medications commonly prescribed to slow the progression of dementia. LeBars et al. found Ginkgo biloba extract effective, but with a side effect profile equivalent to placebo. This well-designed multicenter study showed significantly less decline in cognitive function among patients with dementia receiving ginkgo. They found the dose of 240 mg/day more effective than 120mg (31). They noted, “in contrast to narrow memory tests, broad cognitive assessments were more likely to detect the treatment effect.” Beaubrun and Gray reviewed 40 controlled trials of ginkgo extracts in the treatment of dementia and found that 39 of 40 studies demonstrated clinically significant improvement in memory loss, concentration, fatigue, anxiety, and depressed mood (32). Wong and others found good evidence for the efficacy of ginkgo in the treatment of memory impairment caused by dementia (33). Other studies have also demonstrated significant benefit (34–36).

Side effects of ginkgo biloba are minimal. In a German post-marketing surveillance study of 10,815 patients treated with LI 1370 (another brand of standardized ginkgo), only 183 reported side effects. These side effects included nausea, headache, stomach problems, diarrhea, allergy, anxiety or restlessness, sleep disturbances, and in rare cases, serious bleeding problems. There have been five reports of bleeding associated with ginkgo treatment. These include two subdural hematomas, one with a documented increase in bleeding time, one intracerebral hemorrhage, and one subarachnoid hemorrhage. In most cases, patients were receiving concurrent anticoagulant drugs. Ginkgo reduces platelet aggregation by inhibiting platelet activation factor. Concurrent use of anticoagulants and ginkgo extracts should probably be avoided. It should also be avoided in patients with clotting problems. One case study reported ventricular arrhythmias with Ginkgo (37).

Cochrane reviews conclude there is “promising evidence of improvement in cognition and function associated with Ginkgo”, but recommends larger controlled trials (38). Two randomized, placebo controlled and double blind



trials of ginkgo biloba have been sponsored by the National Center for Complementary and Alternative Medicine (NCCAM). The Ginkgo Biloba Prevention Trial in Older Individuals was a stage III trial set up to determine the effect of 240mg/day Ginkgo biloba in decreasing the incidence of dementia and specifically Alzheimer's disease (AD), slowing cognitive decline and functional disability, reducing incidence of cardiovascular disease, and decreasing total mortality over five years. All subjects were 75 or older and without serious comorbidities. The study is now closed.

The other study, Preventing Cognitive Decline with Alternative Therapies, focuses on the oldest old who are at a particularly high risk for developing mild cognitive impairment (MCI), a precursor to dementia. The effect of standardized ginkgo biloba extract (GBE) on preventing or delaying cognitive decline in people age 85 years or older is studied over 42 months. Not yet closed, they plan to enroll 200 elderly cognitively healthy subjects and follow them for detection of conversion to MCI. The study hopes to definitively examine whether GBE has a disease modifying effect on the brain—distinct from a symptomatic effect. The magnitude of biological effect of the treatments will also be assessed with volumetric quantitative MRI, a complementary means of confirming whether there is a brain modifying effect (measured as a decrease in brain volume loss with treatment). Peripheral markers of oxidation status will measure possible anti-oxidant effects of GBE. The Principal Investigator is Dr. Jeffrey Kaye at the Oregon Health Sciences University in Portland.

*Pyritinol* Pyritinol is used by some to enhance neuronal metabolic function. The pyritinol molecule is structurally similar to vitamin B<sub>6</sub>, but functions in the brain in a different way. The dose of pyritinol used in most of the human clinical studies is one 200-mg capsule taken three times a day.

Fischhoff, et al. reported on a 12-week, double-blind clinical trial that was performed to investigate the benefit of pyritinol in the treatment of several forms of senile dementia (39). A total of 156 patients were allocated to either of two groups: the "senile dementia of the Alzheimer's type" group, or the "multi-infarct dementia (stroke)" group. The investigators noted, "The therapeutic efficacy of pyritinol was clearly demonstrated by confirmatory analysis as the drug was statistically significantly superior to placebo in all three target variables (of cognitive function). The EEG mapping demonstrated significant differences between placebo and pyritinol . . . it can be accepted that the therapeutic effect of pyritinol is superior to placebo in patients with mild to moderate dementia of both degenerative (Alzheimer's) and vascular (stroke) etiology."

A double-blind, placebo-controlled trial was carried out on 40 patients suffering from moderately advanced

dementia. The patients were allocated randomly either pyritinol (800 mg daily) or identical placebo for three months. Assessments using a modified Crichton Geriatric Behavioral Rating Scale were made pre-treatment and monthly up to three months, and then at follow-up at six months. Patients on pyritinol showed significantly higher levels of improvement than did those on placebo. Laboratory tests conducted throughout remained within normal limits for both groups (40).

Another study, reported 26 patients with Alzheimer's disease who were randomly assigned in a double-blind trial of pyritinol versus placebo. The patients had a mild to moderate degree of dementia. The results of the study showed that "pyritinol was associated with a significant improvement in cognitive performance. Regional cerebral blood-flow data showed that treatment with pyritinol normalized the pattern of blood flow increase during activation and improved the score on the test used for activation (41). In the German journal *Pharmacopsychiatry*, the effects of pyritinol were investigated in a placebo-controlled, randomized, double-blind study in geriatric patients suffering from cerebral functional disorders, with a moderate to severe degree of chronic brain syndrome. In a previous study, a rise in the vigilance (wakefulness, alertness) level was demonstrated in patients undergoing pyritinol treatment. Data from 107 patients were included in the statistical analysis, 54 on pyritinol and 53 on placebo. No notable adverse drug reactions were observed. They noted "Statistically significant results were found in favor of pyritinol, compared with placebo, in both the level of clinical symptomatology and the performance level. Particularly impressive was the superiority of pyritinol in the factor 'social behavior'"(42).

One of the few studies that specifically used nutritional supplements in the brain-injured was carried out in the late 1970s by Kitamura in Tokyo. Two hundred and seventy patients suffering from the sequelae of different forms of brain injury were treated orally with pyritinol, 200 mg three times a day, for a period of six weeks. Compared with placebo therapy, pyritinol produced statistically significant improvements in the clinical and psycho neurological manifestations. It was concluded that pyritinol is a drug of therapeutic benefit in the treatment of the sequelae of cerebral trauma (43).

*Piracetam (also nootropil) and Levirpiracetam (the S-enantiomer)* Piracetam has been the subject of multiple animal and human studies. It has been described as a "nootropic" drug due to its putative neuroprotective effects in rat models of brain injury. It has been reported as helpful in cognitive enhancement (44). It has been described as the "number one worldwide cognitive enhancer" on one web site that served to facilitate its procurement (the site has now been closed by federal agents.) A nonblinded polish study was reported in 1998 where

the drug was administered IV or orally to patients with acute brain injury (45). Their conclusion that “the use of piracetam is recommended” is not supported by the study. Ricci reported on its use in acute ischemic stroke and found no demonstration of effectiveness, but a trend of increased mortality in the treatment group (46). Oosterveld reported on benefit in vestibular disorders following brain injury (47). Kessler and others reported in Stroke in 2000 that piracetam facilitates rehabilitation of post stroke aphasic patients (48). Yet, Greener and others, reporting in their Cochrane database review of use of piracetam for aphasia, found a trend toward increased mortality in the treatment group of Kessler’s Study (49). Gualtieri and others questioned study design as the reason for some studies failing to demonstrate effectiveness of piracetam (50). Piracetam is available through foreign pharmacies and/or state side compounding pharmacies.

*Acetyl-L-Carnitine and Vinpocetine* Some nutrients with intriguing findings in human studies and possible value in humans, (44) but which need further study include vinpocetine (51, 52, 53, 54) and acetyl-L-carnitine.

**Vinpocetine, Cavinton, vinpocetine-ethyl-apovincaminat, 14-ethoxycarbonyl-(3alpha,16alpha-ethyl)-14, 15-eburnamine, Apovincaminic acid**

Another biological product with a variety of reputed CNS effects is vinpocetine. Originally synthesized in the late 1960s from an extract of the leaf of the lesser periwinkle plant (*Vinca minor*), vinpocetine was first commercially available in 1978. Marketed as Cavinton by the company Gedeon Richter Ltd in Budapest, the drug has been used widely in Eastern Europe. In fact, most of the literature is in Russian and other Slavic languages.

Vinpocetine is reported to have diverse effects. A Hungarian study noted:

Early experiments with vinpocetine indicated five main pharmacological and biochemical actions: (1) selective enhancement of the brain circulation and oxygen utilization without significant alteration in parameters of systemic circulation, (2) increased tolerance of the brain toward hypoxia and ischemia, (3) anticonvulsant activity, (4) inhibitory effect on phosphodiesterase (PDE) enzyme and (5) improvement of rheological properties of the blood and inhibition of aggregation of thrombocytes. Later studies in various laboratories confirmed the above effects and clearly demonstrated that vinpocetine offers significant and direct neuroprotection both under *in vitro* and *in vivo* conditions (55).

Regarding mechanism, Nicholson summarizes a review of the literature with reference to vinpocetine that

“This compound attenuates cognitive deficits, reduces ischaemia-induced hippocampal cell loss and increases cerebral blood flow and glucose utilisation. These effects may be induced by modulation of cyclic nucleotide levels and adenosine re-uptake inhibition” (Nicholson, CD)(56).

Research published by the manufacturer reported that “vinpocetine is a potent inhibitor of the voltage-dependent Na(+) channels and a selective inhibitor of the Ca(2+)/calmoduline-dependent phosphodiesterase 1.” Their positron emission tomography (PET) scan studies in monkeys and healthy humans using intravenously administered [11C]-labeled vinpocetine showed “the distribution pattern of vinpocetine in the brain was heterogeneous, with the highest uptake in the thalamus, basal ganglia and visual cortex.”(57)

Is there a neuroprotective effect? A British study in normal subjects demonstrated a protective effect against memory impairments caused by exposure to benzodiazepines (58). A study of brain preservation in a rat model of ischemia showing a 42% reduction of infarct volume (59). The drug was even used in 162 victims of the accident at the Chernobyl Atomic Electric Power Station diagnosed with “dyscirculatory encephalopathy” (60). Hadjiev argues it is protective against cerebrovascular insufficiency in humans (61).

Does the drug really work in demented humans? A 2003 review article in Nutrition concluded that it is effective (62). A review of nontraditional medicines by Kidd observed that vinpocetine “is an excellent vasodilator and cerebral metabolic enhancer with proven benefits for vascular-based cognitive dysfunction.”(63) One double-blind placebo controlled trial of the drug over nine months in 84 patients diagnosed with vascular dementia demonstrated the treatment group performed consistently “better in all evaluations of the effectiveness of treatment including measurements on the Clinical Global Impression (CGI) scale, the Sandoz Clinical Assessment-Geriatric (SCAG) scale, and the Mini-Mental Status Questionnaire (MMSQ)”(64). Yet, a yearlong Veterans Administration (VA) study of Alzheimer’s patients found no benefit of vinpocetine at a variety of dosages (65).

A Cochrane database review in 2003 found three trials with a total of 583 people with degenerative or vascular dementia treated with vinpocetine (30–60 mg/day) or placebo (66). The number of patients treated for 6 months or more was small and only one study extended treatment to one year. They noted, “the evidence for beneficial effect of vinpocetine on patients with dementia is inconclusive and does not support clinical use.” The conclusion was the same in a 2000 Cochrane review of its use in acute stroke (65).

The literature supporting the use of vinpocetine in traumatic brain injury (TBI) is even more sparse. One Russian study primarily reporting that diabetics do worse

than others following TBI observed “inclusion of vasoactive agents Cavinton and Complamin into the scheme of complex therapy accelerates regression of the neurological symptomatology” (68). In an experimental study involving animals, Romodanov found that these vasoactive agents “promote regression of the changed cerebral blood flow” following TBI.

In summary, vinpocetine is of equivocal benefit, but there is little evidence of toxicity. Due to research suggesting effectiveness in some groups, further double-blind placebo-controlled studies of its use in specific patient populations is warranted.

#### **DMAE (dimethylamino ethanol), Pantothenic acid, Lucidril, and Citicoline**

Other nutrients are recommended on web sites with little evidence on effectiveness in humans. Based on animal studies (mostly Russian and Japanese from over twenty years ago), these include DMAE (dimethylamino ethanol), pantothenic acid, lucidril, and citicoline.

#### **FOR BEHAVIORAL DISTURBANCES**

*Kava (Piper methysticum)* Kava is widely used in Polynesia and Micronesia as a tranquilizing ceremonial beverage. Kava is one of the few herbs for which active constituents are well delineated. Some are centrally acting skeletal muscle relaxants and anticonvulsants. Their effects seem to be due to inhibition of sodium and calcium channels as well as effects on glutamate systems. Some are potent inhibitors of norepinephrine uptake (4).

A psychoactive member of the pepper family, kava is used to relieve anxiety and insomnia in Europe and the United States. It is formally approved in Germany for anxiety, tension, and agitation. In a randomized, double-blind, placebo-controlled trial, 58 patients with “anxiety and neurotic disorders” were randomly assigned to receive 70 mg of kava lactones or placebo three times daily for 4 weeks. Compared with the placebo group, the kava group demonstrated a significant reduction in anxiety (assessed by HAM-A) by the end of the first week; differences between the two groups increased during the course of the study. Side effects were minimal (69).

In a randomized, double-blind, placebo-controlled multicenter study, 101 outpatients with anxiety disorders (agoraphobia, specific phobia, generalized anxiety disorder, or adjustment disorder with anxiety) were treated with a kava extract for 24 weeks. Results showed significant reductions in HAM-A scores in the kava group beginning in the eighth week and increasing throughout the trial. Improvements were also seen in secondary outcome variables, which included Hamilton subscale scores for somatic and psychic anxiety, the Clinical Global Impression scale,

Self-Report Symptom Inventory, and the Adjective Mood scale (70). Side effects were greater in the placebo group than the kava group. Treatment with kava did not lead to tolerance. Several other controlled double-blind trials on kava extracts or the isolated compound DL-kawain have been published in the German literature (4).

Kava is reported to have potential adverse effects and interactions. Therapeutic doses may result in mild gastrointestinal complaints or allergic skin reactions (incidence, 1.5%) (4). Chronic use of kava up to 100 times the therapeutic dose results in an ichthyosiform eruption known as kava dermatopathy, which is often accompanied by eye irritation. Abstaining from kava results in complete resolution of symptoms. Kava may potentiate the sedative affect of anesthetics (72).

*Picamilon* Picamilon is a vitamin-like compound consisting of a niacin analogue (n-nicotinyl) uniquely bonded to GABA (gamma aminobutyric acid). When niacin is bound to GABA, it readily penetrates the blood-brain barrier and enhances cerebral and peripheral circulation. Picamilon has reportedly been studied and used in Russia or its “tranquilizing influence on negative emotions”. The effects of picamilon have been characterized as “a tranquilizing effect, without a sedative component but with elements of stimulant action.” Doses are reported as 20–50 mg bid or tid. Picamilon has been reported to decrease cerebral blood-vessel tone and “increases intracranial circulation rate”. Picamilon reportedly reduces anxiety and hyperesthesia (whereby normal touch creates pain) without sedative effects, and yet improved sleep. Studies in English are few.

*Ginseng (Panax ginseng and others)* Ginseng is a popular “tonic” herb that some take regularly for a “cumulative strengthening effect”. There are several varieties of ginseng commonly used in herbal medicine: *P. ginseng*, grown in northeastern China and Korea; *P. quinquefolius*, grown in the United States and Canada; and *P. notoginseng*, grown in southwest China. Ginseng reportedly has many interesting effects, but its place in the treatment of psychiatric conditions or improving quality of life has not been demonstrated in clinical trials.

An 8-week, placebo-controlled study of a commercial ginseng among 60 patients admitted to the geriatric unit of a hospital found no differences between the treatment and control groups in length of stay, activities of daily living, cognitive function, or somatic symptoms (73, 80). Yet, a double-blind study of a multivitamin complex supplemented with ginseng vs. a multivitamin complex without ginseng in 625 patients complaining of stress or fatigue found significant improvement in the quality of life index at 4 months in those receiving ginseng (74). Hypoglycemia as well as bleeding complications have been reported with ginseng (72, 75).

*Passionflower (Passiflora incarnata)* Passionflower is used as a mild sedative. No clinical trials of its use as a single agent have been conducted. The German Commission E recommends 4 to 8 g of dried herb per day for “nervous unrest.”

Passionflower contains flavonoids: a flavonoid derived from *Passiflora coerulea*, is a partial agonist of benzodiazepine receptors and has anxiolytic activity in mice without inducing sedation or muscle relaxation and could account for the activity of the plant (4).

In a double-blind trial in 182 patients with adjustment disorder with anxious mood, patients received a preparation containing six extracts (*Passiflora*, *Crataegus*, *Ballota*, *Valeriana*, *Cola*, and *Paullinia*) or placebo. HAM-A scores were improved in patients who took the herbal mixture compared with those who received a placebo (76).

*Valerian (Valeriana officinalis)* Valerian is a botanical medicine used for its mild sedative and tranquilizing properties. Valerian is an odoriferous plant that is a popular sleep remedy. In one study enrolling 166 subjects with various sleep difficulties, two different formulations of valerian were compared to placebo. Each person received three of each capsule, which were taken in random order on non-consecutive nights. Only 128 patients completed the study, but only one patient withdrew because of side effects. Both valerian preparations improved sleep quality and reduced sleep latency scores. Night awakenings and dream recall were not affected by valerian, nor did valerian cause any somnolence the next morning (77). Beaubrun, in a review of the herbal medication literature, noted that: “Valerian has been shown to decrease sleep latency and nocturnal awakenings and improve subjective sleep quality, but placebo effects were marked in some studies, and in some cases the beneficial effects were not seen until two to four weeks of therapy” (Beaubrun G)(78).

Another study found efficacy of both valerian and melatonin (79). Dosing recommendations vary, but the German Commission E recommends 2 to 3 g of the dried root one or more times a day for “restlessness and nervous disturbance of sleep” (80).

A valerian withdrawal syndrome has been described. Garges reported a withdrawal reaction of delirium, and high output cardiac failure in a 58-year-old man hospitalized for congestive heart failure who received general anesthesia. After extubation, the patient developed sinus tachycardia, high output cardiac failure, oliguria, tremor, and signs of delirium. It was later discovered the patient had been taking valerian up to 2 g five times per day for years. A benzodiazepine was helpful in resolving many of his symptoms (81). Also, Valerian may potentiate the sedative effects of anesthetics (72).

Another problem with valerian is its unpleasant odor—one foul enough to be used as the aversive stimulus

in a study of brain activation (71). This interferes with patient tolerance as well as the ability to do double-blinded trials.

*Folic Acid, Vitamin B<sub>12</sub>, S-adenosylmethionine (SAM or SAME) and Mood* Folic acid deficiency is one of the most common nutritional deficiencies in the world and has often been associated with neuropsychiatric disorders (82). Deficiencies of vitamin B<sub>12</sub> and folate both cause similar neurological and psychiatric disturbances, including depression, dementia, and psychosis. Folate deficiency appears most tightly connected with depressive disorders, and cobalamin deficiency with psychosis (83). Contrary to intuition, vitamin deficiencies appear to occur infrequently with eating disorders. Hutto notes: “Clinicians should remain vigilant to the possibility of deficiencies of folate and cobalamin in diverse psychiatric populations” (Hutto)(83).

Normal hematological indices do not rule out B<sub>12</sub> and folate deficiencies. This deficiency may be an overlooked and understudied risk factor for depression. Godfrey in London found that 41 (33%) of 123 patients with acute psychiatric disorders (DSM III diagnosis of major depression or schizophrenia) had borderline or definite folate deficiency (red-cell folate below 200 micrograms/l). These patients took part in a double-blind, placebo-controlled trial of methyl folate, 15 mg daily, for 6 months in addition to standard psychotropic treatment. Among both depressed and schizophrenic patients methyl folate significantly improved clinical and social recovery. The differences in outcome scores between methyl folate and placebo groups became greater with time. The authors wrote: “these findings add to the evidence implicating disturbances of methylation in the nervous system in the biology of some forms of mental illness” (Godfrey)(84).

Several studies have found that up to 35% of depressed patients are folate deficient (84). In elderly patients, the incidence of deficiency may even be higher.

Fava and others examined the relationships between levels of folate, vitamin B<sub>12</sub>, and homocysteine and response to fluoxetine (20 mg/d for 8 weeks) treatment as measured by the 17-item HAM-D in 213 outpatients with major depressive disorder. Subjects with low folate levels were more likely to have melancholic depression and were significantly less likely to respond to fluoxetine (85).

Folate and vitamin B<sub>12</sub> are required for the methylation of homocysteine to methionine and for the synthesis of S-adenosylmethionine. S-adenosylmethionine is involved in numerous methylation reactions involving proteins, phospholipids, DNA, and neurotransmitter metabolism. S-adenosylmethionine (SAM) has antidepressant properties. The commonest neuropsychiatric complication of severe folate deficiency is depression (86). Methylation in the nervous system may underlie the expression of mood and related processes and may be

implicated in some affective disorders. Folate deficiency may specifically affect central monoamine metabolism and aggravate depressive disorders. The folate derivative necessary for the synthesis of serotonin and dopamine, tetrahydrobiopterin, has also been reported to have antidepressant activity (87). Folic acid may be helpful in bipolar disorders.

In a double-blind comparing a daily supplement of 200 mcg folic acid placebo in a group of 75 patients on lithium therapy, folate was shown to enhance the efficacy of lithium. During the trial the patients with the highest plasma folate concentrations showed a significant reduction in their affective morbidity. Patients who had their plasma folate increased to 13 µg/ml or above had a 40% reduction in their affective morbidity. The authors suggested that a daily supplement of 300–400 micrograms folic acid would be useful in long-term lithium prophylaxis (88).

Also called SAME, S-adenosylmethionine is a methyl donor closely linked with folate and vitamin B<sub>12</sub> (cyanocobalamin) metabolism. SAME is required in numerous transmethylation reactions involving nucleic acids, proteins, phospholipids, monoamines, and other neurotransmitters. Bottiglieri at Baylor in Dallas wrote that deficiencies of either folate or B<sub>12</sub> have been found to reduce the synthesis of SAME (and thus its levels) in the central nervous system. They noted: "SAME has antidepressant properties, and preliminary studies indicate that it may improve cognitive function in patients with dementia. Treatment with methyl donors (betaine, methionine and SAME) is associated with remyelination in patients with inborn errors of folate and C-1 (one-carbon) metabolism" (Bottiglieri)(89).

Some feel this is relevant to brain injury rehabilitation. The administration of SAME has antidepressant properties (91, 92). However, there are potential side effects of folic acid and same supplementation. In a randomized, double-blind, placebo-controlled trial of 15 inpatients with major depression, oral SAME induced mania in one patient with no prior history of mania (90). In another study of SAM-treated patients with depression, 89% of bipolar patients switched from depression into an elevated mood state (hypomania, mania and euphoria) and the rest did not respond. Just over half of the endogenous unipolar patients improved and five did not (92). Anecdotally, methionine supplementation has been reported to aggravate schizophrenia. SAME has been reported to cause mild and transient insomnia, nervousness, and lack of appetite, constipation, headaches, heart palpitations, nausea, dry mouth, sweating, and dizziness (93).

Folate has been reported to reduce the effectiveness of several anticonvulsants, potentially leading to seizures (94).

**Tryptophan and 5-HTP** The amino acid, tryptophan, is a precursor of serotonin and has been used increase

brain levels of serotonin. Tryptophan depletion can increase depressive symptoms in patients with major depression and seasonal affective disorder. Studies have shown tryptophan supplementation has positive effects in some depressed patients—particularly those with a relative tryptophan depletion (95). In most cases, tryptophan by itself may be insufficient to boost serotonin levels (96). Thus, SSRI antidepressants are much more efficacious overall. On the other hand, using tryptophan to supplement standard antidepressants has been more successful. Walinder found that 24 depressed patients started on clomipramine improved more rapidly in the symptoms of depressed mood, suicidal intent, depressive thought content, and anxiety with tryptophan supplementation (97). 5-HTP is an intermediate metabolite of the amino acid L-tryptophan in the serotonin pathway. Like tryptophan, 5-HTP is used for depression—in efforts to achieve a higher level in the CNS (98). Tryptophan is converted into 5-HTP by the enzyme tryptophan hydroxylase. This is the rate-limiting step in serotonin synthesis. 5-HTP is commercially produced by extraction from the seeds of an African plant, *Griffonia simplicifolia*—an extract available in the United States. However, there are significant concerns with tryptophan and 5-HTP supplementation. The severe complication of eosinophilic myositis (EMS) has occurred with contaminated tryptophan. It causes muscle pain and weakness (99). While contaminated L-tryptophan has been definitively associated with EMS, 5-HTP has been linked with several unusual cases of EMS-like symptoms. One study suggested that contamination may be difficult to avoid with L-tryptophan and 5-HTP preparations.

## AGGRESSION AND DEPRESSION

**Omega-3 Fatty Acids** Neuronal membranes contain high concentrations of the essential fatty acids arachidonic acid and DHA, which are crucial components of the phospholipid bilayer (each comprises approximately 25% of the phospholipid content).

It has been suggested that depletion of omega-3 polyunsaturated fatty acids, particularly DHA, impairs membrane function and may be of etiological importance in depression, aggression, schizophrenia, and other mental and neurological disorders. Hibbeln writes: "we propose that excessive phospholipase-A2 (PLA2) activity disrupts membrane fluidity, composition, and therefore, the activity, of membrane-dependent proteins. Similar disruptions in these proteins are documented in depressed patients and can be accounted for by excessive PLA2 activity" (Hibbeln)(100, 101).

The number of authors supporting this premise is limited. Yet, lipids and the membranes they inhabit may be very important. There are reports that rapid lowering

of blood lipids by hydroxymethylglutaryl coenzyme A reductase inhibitors is associated with a large number of psychiatric disorders. In a national Norwegian database, 15% of psychiatric drug reactions were attributed to statins (102). Reactions included aggression, nervousness, depression, anxiety, and sleeping disorders. Cholesterol-lowering therapies and low cholesterol levels have been thought to increase the risk of suicide—possibly by lowering serotonin turnover. Therefore, some recommend omega-3 fatty acid supplementation as possibly helpful in brain disorders.

*St John's Wort (Hypericum)* St John's Wort (SJW), also called Hypericum, is one of the most widely-used supplements. In 1998, Wong reported that there was good evidence for the efficacy of St John's wort for the treatment of depression(33) There is data to suggest that St John's wort is more effective than placebo in the treatment of mild to moderate depression. The absolute increased response rate with the use of St John's wort ranged from 23% to 55% higher than with placebo, but ranged from 6% to 18% lower compared with tricyclic antidepressants (103). In 2000, Beaubrun and Gray reported on their review of herbal medicines for psychiatric disorders. They found nine controlled and standardized trials of St. John's wort. Of these, five showed the herb's superiority to placebo, and four found no differences in effectiveness when compared with antidepressant drugs (78). One author reported extensively on its neuropharmacology (3, 104).

Combination therapy may be helpful in combined anxiety and depression. Muller's open labeled study with SJW and valerian concluded that symptoms associated with anxiety that severely afflict patients can be clearly improved more quickly with a combination therapy of St John's wort extract and valerian extract than with St John's wort monotherapy (105). The combination therapy was well tolerated, no significant side-effects occurred. St. John's Wort is metabolized by the P450 system and thus has been reported to interact with several medications.

### NUTRITIONAL SUPPLEMENTS FOR THE TREATMENT OF HEADACHE

Melatonin has been recommended for cluster headaches. In a double-blind, placebo-controlled clinical study of 20 patients, melatonin was reported to effectively reduce cluster headache in 50% of treated patients. In the paper's discussion, melatonin's biological functions are reviewed in relation to the putative mechanisms that cause cluster headache (106). In a more recent review of cluster headaches, Dodrick reported that melatonin may be a useful adjunctive therapy (112).

### Petadolex, *Petasites hybridus*, Butterbur root (a naturopathic agent)

Another agent used for headache is Petadolex (*Petasites hybridus*, an extract of Butterbur root). *Petasites hybridus* (PH) is much more commonly referenced for respiratory problems such as asthma than for headache (107). It is also used to reduce gastrointestinal and urogenital tract spasms. Reportedly, its active components are the petasines which inhibit the synthesis of leukotrienes (anti-inflammatory) and decrease the intracellular concentration of calcium (spasmolytic).

Still controversial, it has been recommended for migraine prophylaxis, but only one blinded study could be identified. A German group reported twice on the same randomized, group-parallel, placebo-controlled, double-blind clinical study of 60 patients. A "special CO<sub>2</sub> extract from the rhizome of *Petasites hybridus*" was administered at a dose of 50 mg b.i.d. for 12 weeks. Although no significant decrement in intensity and duration was observed, a significant 60% reduction in the frequency of migraine attacks was seen. No adverse events were reported (108, 109). Another unaffiliated group reanalyzed the data from that study (110). They looked at the data differently, but still noted a significant reduction in attack frequency—from 3.4 at baseline to 1.8 after three months. They concluded, "This small trial indicates that butterbur may be effective in the prophylaxis of migraine."

A German-language review article observed that toxicity is reportedly infrequent since the development of "extraction with supercritical CO<sub>2</sub> . . . (which reduced) the concentrations of the potentially hepatotoxic and carcinogenic pyrrolizidine alkaloids (to) below the detection limits"(111). Four cases of reversible cholestatic hepatitis have been associated with long-term administration of butterbur. Further side effects involve the gastrointestinal tract and are usually mild.

Other relatively unsupported recommendations for headache include green tea (which contains caffeine)(113) megadose vitamins C, (114, 115) and vitamin E, (116) lipoic acid, and Coenzyme Q at 150 mg/day (117). Gingko biloba has been anecdotally reported to be helpful for those patients suffering from migraine headaches. Another study found it helpful in preventing headache symptoms of acute mountain sickness (118). Oral magnesium is a complementary therapy for headache (119) that has documented efficacy in migraine prophylaxis for children (9mg/kg/day) (120). Recent studies using functional MRI suggest a drop in magnesium concentration may play a role in severe types of headaches (121, 122). In a Brooklyn, NY study, six of nine children with non-traumatic headaches had a deficiency in serum ionized magnesium, (123) but total magnesium levels were normal. The National Institute of Neurological Disorders and Stroke (NINDS) is sponsoring a phase III study of magnesium sulfate given within

eight hours of a moderate or severe traumatic brain injury to look at the effect on survival, seizures, and outcome. <http://www.edc.gsph.pitt.edu/neurotrauma/> .

### NUTRITIONAL SUPPLEMENTS FOR VESTIBULAR DYSFUNCTION

*Gingko biloba* In an open label study of vertigo, ginkgo biloba given over three months improved symptoms of dizziness and also, on neuro-otologic testing, improved several parameter. Improvements were noted in saccadic velocities and smooth pursuit gain, nystagmus, vestibulo-ocular reflex and the visuovestibular-ocular reflex (124).

*Pyritinol* A reference in the French journal *Ouest Med* (29/1 1976), reports that pyritinol was tested on sixty patients who suffered from vertigo. They report “a cure rate of 83%, accompanied by an improvement in the patients’ mental and social state. The drug was tolerated well by patients of all ages.” The dose was 200 mg three times a day (125).

*Piracetam* A 1999 literature review of piracetam recommended doses of 2.4–4.8 gm daily for vertigo of central origin such as after brain injury (47).

*Coenzyme Q10 (ubiquinone)* Much of the extent of neurological impairment following brain injury depends upon secondary brain damage, with delayed neuronal death. Some stroke research suggests that secondary brain damage follows from secondary mitochondrial (and bioenergetic) failure after blood flow resumes.

Recent evidence points to programmed cell death as a major factor in delayed neuronal death. While this programmed cellular suicide normally disposes of aged cells, stroke may trigger it prematurely. Mitochondrial injury following ischemia leads to calcium overload, excitotoxicity, oxidative stress, and opening of the mitochondrial mega channels.

Medications that support normal cellular energy production and antioxidant defense could protect against this excitotoxic damage and subsequent programmed cell death. Some studies suggest CoQ10 may provide this protective effect (126–129).

*Creatine* Of all the nutritional supplements currently available, creatine appears to be the most effective for maintaining the ability of mitochondria to produce high-energy compounds such as adenosine triphosphate (ATP) and thus reduce “oxidative stress.”

When ATP loses a phosphate molecule and becomes ADP, it must be converted back to ATP to once again be able to release energy. Creatine is stored in the human body as creatine phosphate (CP). Then ATP is depleted,

it can be “recharged” by CP. CP donates a phosphate molecule to ADP allowing it to form a high-energy bond and reform ATP. An increased pool of CP means faster recharging of ATP, which means more work can be performed.

Creatine may protect the brain from neurotoxic agents, certain forms of injury and other insults. Neurons exposed to either glutamate, beta-amyloid (both highly toxic to neurons) are involved, (130) N-methyl-D-aspartate (NMDA) and malonate(131) (Another study found that feeding rats creatine helped protect them against tetrahydropyridine (MPTP), which produces parkinsonism in animals through impaired energy production (132). Another study found creatine protected neurons from ischemic damage (133).

### NEUROPROTECTIVE ROLE OF CURCUMIN FROM CURCUMA LONGA ON ETHANOL-INDUCED BRAIN DAMAGE

*Curcumin* A widely used spice and coloring agent in food, curcumin has been shown to possess potent antioxidant, antitumor promoting and anti-inflammatory properties in vitro and in vivo. Curcumin is a small-molecular-weight compound that is isolated from the commonly used spice turmeric. In an animal study, curcumin was screened for neuroprotective activity using ethanol as a model of brain injury. Oral administration of curcumin to rats caused a significant reversal in lipid peroxidation of brain lipids and produced enhancement of glutathione, an antioxidant (134).

### VITAMIN SUPPLEMENTATION TO FACILITATE NEUROLOGICAL RECOVERY

Vitamin (MVI) supplementation is controversial. Certainly the minimum daily requirement of MVI is needed for normal enzyme function. Earlier in this paper, effects of folic acid and vitamin B<sub>12</sub> deficiencies and supplementation were discussed. However, some physicians feel that megavitamin supplementation of water-soluble vitamins is a waste – producing “only an expensive urine”. Yet, the true need may vary between individuals and in disease states. High doses of Vitamin B<sub>6</sub> (50–200 mg) are commonly used in carpal tunnel syndrome. By analogy, some physicians feel it is helpful in other types of nerve injury. Yet, in the example of Vitamin B<sub>6</sub>, megadose (2000 mg<sup>+</sup>) can itself be neurotoxic (135).

Suggested supplements from physicians who prescribe for neural recovery following brain injury include vitamin B<sub>1</sub> (100 mg), vitamin B<sub>6</sub> (100 mg), vitamin B<sub>12</sub> (1 mg), folic acid (1 mg) and vitamin C (500 mg). Also recommendations for myelin repair are octacosanol (2000–400 mg/day) with zinc, vitamin C and B<sub>6</sub>. (Internet communication from

William Walsh, PhD re: study at Schwab Rehab Hospital—reportedly facilitating recovery after plateau in severe brain injury).

### NUTRITIONAL SUPPLEMENT TO RETARD MUSCLE ATROPHY

In the setting of hypoglycemia, glutamine is the primary gluconeogenic amino acid. Aggressive glutamine supplementation is recommended to help maintain muscle mass for those critically ill or immobilized with severe brain injury.

However, extra caution is recommended in diabetics due to abnormal glutamine metabolism. Adding taurine may be beneficial.

### WEB SITES OF INTEREST

Several studies looking at internet web sites for information about a variety of topics have determined that most offer limited and biased information of poor quality with most claiming to prevent, diagnose, treat, or cure specific diseases despite federal regulations prohibiting statements of this type (136, 137). Nevertheless, some sites have been determined to be particularly helpful in the investigation of dietary supplements. In a study conducted by the College of Pharmacy at the University of Michigan, the best electronic databases for providing information on herbal and dietary supplements were felt to be “Micro Medex” and the “Natural Medicine Comprehensive Database” (138). The best internet site was determined to be “The Natural Pharmacist”. Another fine site is a review article on natural medications in *Psychosomatic Medicine*: <http://www.psychosomaticmedicine.org/cgi/content/full/61/5/712>

The interest in and use of nutritional supplements by the public has grown faster than the definitive medical knowledge of these drugs. Yet there is fairly extensive bench and some clinical research for many of them. Few studies have been done using these medications in patients with traumatic or anoxic brain injury. Yet much of what is known may be relevant to these populations. Desperate patients and families will look to their physicians for direction on optimal treatment. Greater physician knowledge of the benefits and results of the nutritional supplements will lead to better care.

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# 56

## Traditional Chinese Medicine Theory in the Mechanism and Treatment of TBI

Gary G. Wang

### INTRODUCTION

The theory of traditional Chinese medicine (TCM) is completely different from that of western medicine. The formation and development of TCM theory was greatly influenced by ancient Chinese philosophy. It is necessary to explain some basic TCM theories that developed over the past 3000 years before going into its specific applications in traumatic brain injury (TBI) management.

The theories of “*Yin-Yang*” and “The Five Elements” were two approaches to the study of nature in ancient China. Every object or phenomenon in the universe was thought to consist of two opposite yet interdependent parts known as *yin* and *yang*. The theory of the five elements on the other hand, held that wood, fire, earth, metal, and water constituted the physical world. Like *yin-yang*, the five elements were interdependent and inter-resistant. Both theories described the world in a state of constant change between balance and imbalance. Ancient Chinese physicians believed in the integration of the natural world with the bodies of human beings. Diseases were believed to be caused by imbalance among *yin-yang* and the five elements.

As with natural phenomena, ancient Chinese physicians classified human organs and emotions as belonging to one of the five elements. The laws pertaining to

the inter-promoting, interacting, over-acting and counter-acting of the five elements were used to interpret the relationship between the physiology and pathology of the human body. “*Zang-fu*” refers to the gross anatomical entities of the internal organs. However, its meaning is different from that of modern anatomy. The term *zang-fu* is a generalization of the physiological functions of the human body. The heart, liver, spleen, lung, kidney and pericardium are known as the six *zang* organs. They are related to *yin*. Their main physiological functions are to manufacture and store essential substances including vital essence, *qi* (vital energy, pronounced “Chee”), blood, and body fluid. The small intestine, gall bladder, stomach, large intestine, urinary bladder, and *Sanjiao* are known collectively as the six *fu* organs. They are related to *yang*. *Sanjiao* is the name of a function without body shape structure. The main functions of *fu* organs are to receive and digest food, absorb nutrients, and transmit and excrete wastes.

The brain and uterus are two extraordinary *fu* organs. They are closely related to the other regular organs. According to TCM theory, the essence of the kidney produces the marrow that forms the brain as “a sea of marrow.” The brain performs thinking and memorization functions. The heart is the main organ that dominates the mental activity of the brain. The heart, protected by pericardium, governs mental activities and

generally handles the physiological function of the brain as it “houses the mind.” Meanwhile the liver is also related to mental activities by regulating the unrestraint and patency of vital functions. The lung and spleen interfere with mental activity indirectly. The lung promotes the diffusion of *qi*, blood and body fluid into every portion of the body. The spleen supplies nourishment essential to heart and lung, keeps the blood circulating inside the vessels. Dysfunction of *zang* and *fu* will prevent the proper functioning of the brain. Conversely, disorders of the brain will also interfere with the function of *zang* and *fu*.

The channel doctrine is also essential for TCM theory. Meridian channels and the collaterals (Jing and Luo) are the pathways of *qi*, blood and fluid circulation. Meridian channels are the main routes while collaterals are the branches of the channels that connect internal organs as well as limbs to make the whole body into an entity. Each meridian channel comes from different *zang* or *fu* organs and distributes in the trunk and limbs. Channels and *zang fu* viscera are shown on the superficial human body at specific acupuncture points. Through these points, *qi* may be infused into the channels to promote balance in the body. The points are also the places where disease evils can easily pass through. This explains why acupuncture points are always selected as therapeutic locations. Acupuncture is a TCM therapy method to remove obstructions in the meridian channels and to regulate blood and *qi* by stimulating the points with needles. According to the philosophy of TCM, medications and treatment procedures facilitate the rebalance of the human body by altering its constituents.

Ancient Chinese physicians recognized and classified medications (most of these herbs) mainly by observing the effects of their clinical application. By performing numerous experiments, each medical herb was classified to either *yin* or *yang* and was characterized as belonging to one of the five elements with the ability to target different organs. The characteristics and functions of Chinese herbs were described in the book *Compendium of Materia Medica*, which was written by Li Shi-Zhen (1518–1593 A.D.). The process of prescribing the appropriate herbal prescription is a systematic technique developed over thousands of years starting with the analysis of clinical information collected from the patient by observation, auscultation, interrogation, and palpation of the pulse. A TCM physician will diagnose the location and nature of the major unbalanced elements and then prescribe an appropriate formula (combination) of herbs. There are several medical herbs in each formula and each of them may have a different function. Certain combinations of herbs work efficiently to target certain disease conditions and fulfill pharmacology functions. The effect of each formula has been documented through clinical verification and may be adjusted accordingly. A special name is given to each established formula. Thousands of

years of successful clinical treatment applications have produced many herb formulas that are still in use today.

Following, is an introduction to the classification of brain injury and TCM disease elements by organ system which includes prescription formulas available in China as pills widely used in the management of disorders related to TBI. The precise makeup of these prescriptions is too vast to include here, but can be researched using the name. Acupuncture management for traumatic brain injury will also be briefly discussed.

### Acute Severe TBI: Consciousness and Qi Disturbance

TCM physicians differentiate and classify TBI patients into different syndromes according to their clinical symptoms. TCM physicians believe that traumatic injury will rupture the integrity of the natural protection system, permitting the invasion of evil factors, leaking essential *qi*, blood and fluids and inducing blood extravasation. All of these will directly disturb normal *qi* and blood circulation and induce pain. The brain is considered the cleanest organ. It is polluted by trauma, which facilitates the invasion of external pathogenic factors. After severe head trauma, evil factors will attack *zang-fu* organs, blocking the *qi* aperture of the heart and hurting the *qi* that acts as the primary motive force for life activities. TCM physicians usually differentiate and classify acute severe TBI patients into two syndrome-specific groups according to the patient's clinical symptoms, named *qibi* (blockage of *qi*) and *qituo* (exhaustion of *qi*). Because such cases are critical, the modern TCM physicians will usually suggest combined management with modern western medical methods.

*Blockage of Qi* *Qibi* symptoms include unresponsiveness, severe confusion, agitation, delirium, restlessness, flushed face, twitching, and tachypnea. A yellowish sticky film coats the tongue. The pulse is rapid and deep. The focus of treatment of *qibi* is to remove the pathogenic factors blocking the aperture of the heart. Some patients may have fever, flushed faces and be agitated. TCM believes that fever is caused by hot evil *qi* that blocks the function of the brain. An-Gong-Niu-Huang-Wan (安宫牛黄丸), Zi-Xiu-Dan (紫雪丹), and Zi-Bao-Dan (至宝丹) are the medications usually applied. These medications are also used for coma or severe agitation due to other etiologies such as stroke, high fever, meningitis, or encephalitis. An-Gong-Niu-Huang-Wan, is the pill most commonly prescribed. Its extracts for intravenous injection, named Xing-Nao-Jing (醒脑静), are available in China. Several preliminary controlled studies have shown the effectiveness of the intravenous application of Xing-Nao-Jing to treat the comatose state (1–3). As like other TCM medications, the chemical contents of An-Gong-Niu-Huang-Wan are

**TABLE 56-1**  
**TMC Diagnosis and Treatment of Acute Severe TBI**

DIAGNOSIS	MANIFESTATION	TMC TREATMENT
Blockage of Qi	unresponsiveness, severe confusion, agitation, delirium, restlessness, flushed face, fever, yellowish tongue with sticky coat, rapid and deep pulse	<i>Decoction</i> An-Gong-Niu-Huang-Wan Zi-Xiu-Dan Zi-Bao-Dan <i>Acupuncture methods</i> Stimulating the points of the GV Channel on head combined with points on limbs, slightly bleeding the points on terminal digits.
Exhaustion of Qi	deep coma, loss of jaw control, lost bladder control, heavy perspiration, cooling distal limbs, whitish coat of tongue, weak pulse	<i>Decoction</i> Shen-Fu-Tang adding San-Qi  <i>Acupuncture methods</i> Applying moxibustion and/or retaining needles to points of the Ren Channel adding stimulating at CV4, CV6, CV8.

complicated. The exact mechanisms of their effects on acute brain injury are not clear from Western biomedical views. However, recent scientific studies have provided some clues. For example, Niu-Huang (Bos Calculus), one of the major contents of An-Gong-Niu-Huang-Wan is bovine gallstone, a mixture of bilirubin metabolites and endogenous bile acids. After traumatic brain injury and stroke, massive bleeding could produce significant iron-mediated oxidative stress, programmed cell death (apoptosis), and neurodegeneration. Bilirubin metabolites were found to be potent endogenous antioxidants with neuroprotective effects (4–6). One of the major endogenous bile acids, tauroursodeoxycholic acid, was found to have the ability to modulate cell death by interrupting classic pathways of apoptosis and has wide-ranging neuroprotective effects after brain injury (7). However, because the formulation contains small amounts of arsine and mercury, the authors do not recommend the prolonged use of An-Gong-Niu-Huang-Wan.

The acupuncture methods for treating the syndrome of *qi* blockage promote resuscitation by stimulating the points of the Governor Vessel Meridian (GV Channel). Renzhong (GV 26) and Baihui (GV 20) are the two points most often selected. Usually, Yongquan (KI 1) is the point added to “conduct the evil factors down.” The points at the distal fingers including Shaoshang (LU 11), Shaochong (HT 9), Shaoze (SI 1), Zhongchong (PC 9), Shangyang (LI 1), Guanchong (TE 1) are often selected for slight bleeding. In addition, Taichong (LR 3), Fenglong (ST 40), Laogong (PC 8) are sometimes stimulated.

*Exhaustion of Qi Qituo* by severe traumatic brain injury is a very serious and critical condition. The major

symptoms include deep coma with unresponsiveness, loss of jaw control with spontaneous mouth opening, heavy perspiration, lost of bladder control, and distal limb cooling. The tongue coat becomes whitish. The pulse is weak. Management of *qituo* is aimed at consolidating vital energy. TMC physicians prepare a formula by combining Shen-Fu-Tang (参附汤, a decoction of Ginseng and prepared Aconite) with powder of San-Qi (Radix Notoginseng). Acupuncture is also applied frequently for exhaustion of *Qi* to recapture *yang* and avert the collapsing status. Applying moxibustion to points of the Ren Channel is the traditional way. Guanyuan (CV 4), Qihai (CV6) and Shenjue (CV8) are the points for emergency measures to restore vital function. Continuous indirect moxibustion with salt and/or retaining needles for 30 minutes at these points is the traditional method.

### Subacute TBI management with TCM

In TCM, diagnosis and treatment is based on clinical symptoms. Different diseases with similar clinical pictures usually are treated in similar ways. Meanwhile, the same disease with different clinical symptoms may be treated in different ways. Because of the clinical similarity, the management of TBI is quite similar to the treatment of stroke. After the crisis acute stage, in cases of prolonged comatose status, An-Gong-Niu-Huang-Wan and Su-He-Xiang-Wan (苏合香丸, Storax Pill) are often used for resuscitation. Acupuncture methods for coma cases are similar to that for *qi* blockage and additional appropriate points are added according to clinical symptoms present. TCM physicians will apply acupuncture by combining the local and distal points according to the courses of the

**TABLE 56-2**  
**TCM Management of Neural Deficits after Severe TBI**

SYMPTOMS	DECOCTION	ACUPUNCTURE
Prolonged comatose status	An-Gong-Niu-Huang-Wan Su-He-Xiang-Wan	Similar to <i>qi</i> blockage
Aphasia	Ren-Shen-Zai-Zao-Wan	GV15, CV 23, HT 5
Paresis	Huo-Luo-Dan	GV 20, GV16, BL 7 and the points of <i>yang</i> Channels of the affected side. <i>upper limb paralysis</i> LI 15, LI 11, LI 10, TE 5, LI 4 <i>lower limb paralysis</i> GB 30, GB 34, ST 36, ST 41, BL 60 <i>facial paralysis</i> CV 17, ST 4, ST 6, GB 14, LI 4, SI 18, ST 7

channels. For example, because the Large Intestine Channel and Stomach Channel traverse the cheek, Jiache (ST 6), Xiaguan (ST 7) and Hegu (LI 4) are the points to be stimulated for those coma patients with clenched jaw. According to TCM theory, functionally the tongue is related to the heart. Aphasia is a symptom of heart function disorder. Ren-Shen-Zai-Zao-Wan (人参再造丸, Ginseng Restorative Bolus) is the often used to benefit heart *qi*, blood circulation, and promote recovery of aphasia. Yamen (GV15) and Lianquan (CV 23) are local and adjacent points of the tongue. Tongli (HT 5) is the Luo (connecting) point of the Heart Channel. These points are often selected to relieve stiffness of the tongue and treat aphasia and dysarthria. A small control study on TBI aphasia patients showed the functional recovery of the acupuncture treatment group was much better than that of the control group (8).

TCM believes that paresis is a mobility function deficit due to obstruction of *qi* and blood circulation in Channels. Huo-Luo-Dan (活络丹) is one of the popular TCM pills used in hemiplegia cases to remove obstruction and readjust *qi* and blood circulation. Acupuncture is widely used in China to promote the recovery of hemiplegia. The *Yang* Channels of the affected side are the main points to puncture. Points of the healthy side may be added also. Usually, TCM practitioners puncture the healthy side first and then the affected side. Moxibustion may be applied as a supplement. Baihau (GV 20), Fengfu (GV16), and Tongtian (BL 7) are commonly used for all paralysis cases. Jianyu (LI 15) Quchi (LI 11), Shousanli (LI 10), Waiguan (TE 5), and Hegu (LI 4) are usually selected for upper extremity affected cases. Huantiao (GB 30), Yanglingquan (GB 34), Zusanli (ST 36), Jiexi (ST 41), and Kunlun (BL 60) are used for lower limb paresis. Yifeng (CV 17), Dicang (ST 4), Jiache (ST 6), Yangbai (GB 14),

Hegu (LI 4), Quanliao (SI 18), and Xiaguan, (ST 7) are usually added for cases of facial paralysis.

Prescription of traditional Chinese medications is usually made according to a TCM diagnosis based on clinical symptoms. Following are the TCM diagnostic syndromes, most often seen in the subacute TBI cases. The prescriptions will be briefly introduced accordingly.

**Stasis of Blood** Stasis of blood is one of the key etiologies in the TCM brain injury model. TCM theory dictates that the heart houses the mind. Traumatic brain injury may disturb the blood and *qi* circulation and interfere with heart function. Injury may directly induce the stasis of blood. The invasion of external pathogenic factors due to trauma may also interfere with blood circulation and induce stasis. Stasis of blood will interfere with *qi* movement. Pain usually comes from insufficiency or blockage of local *qi* circulation. As “the heart houses the mind”, blood stasis results in a decreased level of consciousness. Consequently, these cases usually have headache and cognitive deficiency. Many TBI cases with symptoms of migraine-like headache are due to blood stasis. Usually, the patient complains of persistent pricking or stabbing headache in a fixed location. A purple tongue or purple spots on the tongue may be seen. The pulse is stringy and hesitant. Promoting blood flow to remove blood stasis is the focus of treatment. Xue-Fu-Zhu-Yu Tang (血府逐瘀汤) and Shu-Jing-Huo-Xie Tang (疏经活血汤) are among the most widely prescribed TCM formulas for those cases of blood stasis with headache and/or other neuralgia. Recent research has confirmed the beneficial effects of these groups of Chinese medicines on neural regeneration. It was reported that after the extracts of Shu-Jing-Huo-Xie Tang were added in a culture medium of neural cells, the neurite outgrowth induced by nerve growth factor (NGF)

increased approximately 30-fold compared to NGF alone (9). Ci-Wu-Jia (Radix Acanthopanax Sceticosi) is one of the herbs prescribed for this type of patient either individually or combined with other TCM medications. Animal studies have demonstrated the strong anti-inflammatory and antinociceptive activities of Acanthopanax Radix extract (10) and its effects as an agent in the prevention of multiple organ dysfunction (11). Acanthopanax Radix is also known to have healing and protective effects on stress-induced disturbances of mental status. Animal studies have suggested that Acanthopanax Radix may act by regulating noradrenaline (NA) and dopamine (DA) levels in specific brain regions related to the stress response (12).

*Deficiency of Qi and Stagnancy of Blood* According to TCM theory, the brain is an organ belonging to *yin* and collecting clean *qi* of *yang*. The function of the brain depends on momentum of *yang-qi*. Some subacute TBI patients show weakness of *qi* as their major clinical phenomena. Deficiency of *qi* can induce stagnancy of blood. Fatigue and headache are the major complaints. The patients look tired with low voices. They have a dull headache, aggravated by fatigue, accompanied by lassitude, lack of strength, anorexia, palpitations, shortness of breath, and sometimes aversion to cold with cool limbs. The tongue shows a thin white coat. The pulses are “thready” and weak. Most TBI cases with hypopituitarism would be classified in this syndrome group. Promoting blood circulation by invigorating *qi* is the method of treatment. Bu-Yang-Huan-Wu-Tang (补阳还五汤), Yi-Qi-Hua-Yu-Tang (益气还五汤) and Taohong Siwu Tang (桃红四物汤, Decoction of Four Ingredients with Peach Seed and Safflower) are among the classic decoctions prescribed to TBI patients for promoting blood circulation by invigorating *qi*. A large-scale clinical case report on the management of subacute or chronic subdural hemorrhage patients with Yi-Qi-Hua-Yu-Tang showed significant therapeutic effects (13). It was reported that Bu-Yang-Huan-Wu showed beneficial effects on disturbance of the hypothalamus-pituitary-thyroid axis after brain ischemic injury (14). Animal studies found that Bu-Yang-Huan-Wu may protect brain neurons from apoptosis after cerebral ischemia. The mechanism may be related to its effects on the improvement of cerebral energy metabolism, regulation of nitric oxide synthesis and antagonism of toxic excitatory amino acids (15). The Taohong Siwu Decoction is effective in hydroxyl radical scavenging and is effective in inhibiting lipid peroxidation (16).

Astragalus root, Chinese angelica root, Ligusticum chuanxiong rhizome, and safflower are the common ingredients among these decoctions. Astragalus, Chinese Angelica, and Ligusticum Chuanxiong have demonstrated a wide range of immunopotentiating and immunomodulating effects (17–19). Angelica Sinensis,

Ligusticum Chuanxiong, and safflower have also showed anti-inflammatory and antioxidizing effects. They could improve brain microcirculation through inhibiting thrombus formation and platelet aggregation as well as blood viscosity active components (20–22). Laboratory studies have also suggested that chaunxiong and safflower have brain neuroprotective effects (23–25).

*Kidney Insufficiency* Insufficiency of the kidney is a contributing factor in some of the post brain injury syndrome cases, especially among the geriatric population. Kidney insufficient patients usually complain of a constant dull headache, with a feeling of emptiness often worsening with exercise. Common accompanying symptoms include lassitude, debility, aching, weakness of the lower back and legs, forgetfulness, decreased intelligence and impotence. The patient often has a reddened tongue with little or no film. The pulses are deep, thready, and weak. There are two kinds of kidney insufficiency, *yin* and *yang*. Cases of the kidney *yin* insufficiency are usually accompanied by dizziness, tinnitus, dry mouth, flushed cheeks, and a hot sensation in the palms and soles. Liu-Wei-Di-Huang-Wan (六味地黄丸, Six Flavor Tea, Rehmannia Pill, LWDH) and Jin-Gui-Shen-Qi-Wan (金匮肾气丸) are the TCM decoctions given most widely. Insufficiency of the kidney-*yang*, is usually accompanied by aversion to cold, cold limbs, nocturia, and pale complexion. The tongue is pale and corpulent with a thick whitish coating. In these cases the TCM physician will usually prescribe kidney *yang* reinforcing medications such as You-Gui-Wan (右归丸) and Shen-Qi-Wan (肾气丸). The contents of LWDH are the main components for the formulas of all the kidney insufficiency prescriptions. LWDH has been widely studied. Recent animal studies have shown that LWDH possesses anti-amnesia effects and memory enhancing properties (26). It was suggested that LWDH corrects the abnormal expressions of hippocampal genes in dementia animals (27). Traditionally, kidney tonic Chinese medications containing LWDH are used widely for general health condition improvement. Those medications are able to enhance non-specific immunology activities (28). LWDH is able to improve immune function by regulating the ratio of T and B cells and control over-expression of cytokine genes from activated mononuclear cells (29–32). In addition, the compounds in LWDH may also protect tissues and organs from cytotoxic attack by noxious reagents (33–34). Dihuang (Radix Rehmanniae), one of the major ingredients of the kidney tonic formulas is also reported to have effects on intelligence enhancement (35).

*Liver Dysfunction* The liver dominates unrestrained *qi* and maintains the patency of *qi* flow. Acute or subacute brain injury may alter liver function by changing the balance of liver-*yang* and of endogenous wind in the liver. Exuberance of liver-*yang* results in a headache characterized by cramping pain in the temple and vertex and is



**TABLE 56-3**  
**Subacute TBI TMC Differential Diagnosis and Decoctions Used Often**

DIAGNOSIS	MANIFESTATIONS	DECOCTION
Stasis of blood	migraine-like headache and cognitive deficiency, purple or purple spots on the tongue, stringy and hesitant pulse	Xue-Fu-Zhu-Yu Tang Shu-Jing-Huo-Xie Tang
Deficiency of qi and stagnancy of blood	fatigue, dull headache, low voices, lassitude, anorexia, palpitations, shortness of breath, aversion to cold, cool limbs, thin whitish coated tongue, thready weak pulse	Bu-Yang-Huan-Wu-Tang Yi-Qi-Hua-Yu-Tang Taohong Siwu Tang
<i>Kidney Insufficiency</i>	constant dull headache with a feeling of emptiness, lassitude, debility, aching and weakness of the lower back and legs, forgetfulness, decreased intelligence	<i>kidney yin insufficiency</i> dizziness, tinnitus, dry mouth, flushed cheeks, and a hot sensation in the palms and soles, reddened tongue with little or no coat, deep and weak pulse
		<i>kidney-yang insufficiency</i> aversion to cold, cold limbs, listlessness, impotence, nocturia, pale complexion, spontaneous perspiration, pale and corpulent tongue with thick whitish coat, weak pulse
<i>Liver Dysfunction</i>	cramping headache in temple and vertex aggravated by anger. faintness, giddiness, insomnia, bitterness in mouth, decreased self-control, irritability, restlessness, insomnia, tremors, twisting of the body, and localized or generalized convulsions, thin yellow coated tongue, a stringy rapid pulse	Tianma Gouteng Yin

aggravated by anger. The headache is often accompanied by faintness, giddiness, dizziness, insomnia, and bitterness in the mouth. Alterations of endogenous wind in the liver cause disturbances of emotions and body movements. Wind is always moving and changing reflecting the patient's symptoms of decreased self-control, irritability, restlessness, and insomnia. The patient may have abnormal body movements such as tremors, twisting of the body, and localized or generalized convulsions. Patients have a thin yellow tongue coating and a stringy rapid pulse. TMC management is oriented at subduing the exuberant *yang* of the liver in turn calming the internal wind. Tianma Gouteng Yin (天麻钩藤, Decoction of Gastrodia and Uncaria) is the formula most commonly prescribed for these patients. Tianma (*Gastrodia elata* Bl.) and Gouteng (*Uncaria rhynchophylla* Jack) are traditional Chinese herbs that are used to treat convulsive disorders such as epilepsy. Synergistic anticonvulsive effects were observed in animal studies (36). Gastrodia is widely used by TCM physicians to manage headache, dizziness, vertigo, dementia, and convulsions (37). Pharmacological studies have shown that the anticonvulsive properties and brain neuronal protective effects of the constituents of Gastrodia are related to their free radical scavenging activities and modulator effects on neurotransmission

(36, 38–41). The cognitive beneficial effects of *Castrodia* and its ability to improve learning and memory have been confirmed by animal studies (42–44). Interestingly, animal studies have also shown that motion sickness can be treated with *Gastrodia* (45).

### Chronic Post-TBI Syndrome:

Patients suffering from brain concussion, brain contusion, and traumatic intracranial hemorrhage may have residual symptoms of post brain injury syndrome such as headache and dizziness. TCM physicians divide cases of post brain injury syndrome into several types according to the accompanying symptoms. The treatment methods may be the same for different diseases that share similar clinical pictures.

*Qi*, blood and body fluids are fundamental substances in the human body. They sustain normal vital activities. Their existence and function are generally manifest in the functional activities of various tissues and organs. Blood and *qi* are closely related. The formation and circulation of blood depends upon *qi*, while the formation and distribution of *qi* is intimately absorbed in blood. TCM physicians believe, as a result of endogenous injury, the chronic post brain injury syndrome is due to

the unbalance of *qi*, blood, and body fluid. Trauma and prolonged morbid status would excessively consume *qi*, blood, and fluid essence and induce *qi* deficiency. Patients with *qi* deficiency will complain of a dull headache, which is aggravated by fatigue, accompanied by lassitude, lack of strength, anorexia, palpitations, and shortness of breath. A thin white tongue coating and thready weak pulse is usually found. Buzhong Yiqi Wan (补中益气丸) is the formula of choice to replenish *qi*. Post-brain injury patients with general blood deficiency usually have headache, dizziness, palpitations, insomnia, dreamful sleep, blurred vision, numbness of the limbs, pale tongue, and “thready” pulse. Siwu Tang (四物汤, Decoction of Four Ingredients) is the basic formula used to nourish the blood. Siwu Tang plus Flos Chrysanthemi (chrysanthemum flower) and Fructus Viticis (chastetree fruit) is a treatment for blood deficiency patients with headache as their major complaint. Those patients with symptoms of both *qi* and blood deficiency receive Renshen Yangyin Wan (人参养阴丸, Geinseng Nutrition Pill) and Shiquan Dabu Wan (十全大补丸, Bolus of Ten Powerful Tonics). Excessively consuming essence fluid of the kidney will induce kidney *yin* deficiency. For those post brain injury cases with *yin* deficient phenomena as described previously, Qi Ju Dihuang Wan (杞菊地黄丸, LWDH with Wolfberry and Chrysanthemum) is often prescribed.

Some cases with poor general health may also show symptoms similar to liver *yang* disturbance. Liver *yang* hyperactivity may be secondary to a relative *yin* deficiency. Nourishing *yin* and calming down *yang* is the strategy for treatment with Liu-Wei-Di-Huang-Wan and Zhengan Xifeng Wan (镇肝熄风丸). TCM physicians believe the liver aids the spleen and stomach in digestion and absorption. Trauma may disturb liver *qi* leading to digestive disorders manifested as nausea, anorexia, abdominal distention, acid regurgitation, loose stool, etc. Female patients may have irregular menstruation. For cases accompanied by liver-*yang* hyperactive symptoms described previously, Longdan Xiegan Wan (龙胆泻肝丸) is administered. Post-TBI patients with deficiency of the liver-*qi*, usually have a coexisting deficiency of blood in the liver. This manifests as pallor of the face and lips, lassitude, tinnitus, deafness, and liability to panic. Dan Zhi Xiaoyao Wan (丹栀逍遥丸) is a medication often given (Table 56-4).

The acupuncture management strategies of post-TBI syndromes are also formulated according to clinical complaints and symptoms. Among the various post-TBI clinical symptoms, headache is one of the most common complaints. We hereby discuss headache as an example to introduce the basic acupuncture treatment methods of post-TBI symptoms. TMC theory relates that the head is the place where all the *yang* channels of the upper and

**TABLE 56-4**  
*Chronic Post-TBI Syndrome TCM Differentiation and Treatment*

TYPES	MANIFESTATION	DECOCTION SUGGESTED
<i>Qi</i> deficiency	dull headache, aggravated by fatigue; lassitude, anorexia, palpitations, shortness of breath, thin white coated tongue, thready and weak pulse	Buzhong Yiqi Wan
Blood deficiency	headache, dizziness, palpitations, insomnia, dreamful sleep, blurred vision, numbness of the limbs, pale tongue, thready pulse	Siwu Tang
Both <i>qi</i> and blood deficiency	as above combined	Renshen Yangyin Wan Shiquan Dabu Wan
Kidney <i>yin</i> deficiency	lumbago, lassitude, dizziness, tinnitus, nocturnal emission, premature ejaculation, dry mouth, sore throat, flushed cheeks, hot sensation in palm and sole, reddened tongue with little or no coating, thread and rapid pulse	Qi Ju Dihuang Wan
Liver <i>yang</i> hyperactivity	cramping headache over temple and vertex, intermittent dizziness, giddiness, restlessness, irritability, insomnia, bitter taste, taut pulse	Liu-Wei-Di-Huang-Wan and Zhengan Xifeng Wan
Disturb liver <i>qi</i>	nausea, anorexia, abdominal distention, acid regurgitation, loose stool, irregular menstruation	Longdan Xiegan Wan
Deficiency of the liver- <i>qi</i> ,	pallor of the face and lips, lassitude, tinnitus, deafness, liability to panic	Dan Zhi Xiaoyao Wan

**TABLE 56-5**  
*Acupuncture Point Selection for Chronic Post-TBI Headache*

REGION OF HEADACHE	CHANNEL OF DISTAL POINT SELECTED	PRESCRIPTION EXAMPLE
Occipital	Urinary Bladder Channel of Foot – Taiyang	GB 20, BL 10, BL 60
Forehead and supraorbital	Stomach Channel of foot-Yangming.	ST 8, GV 24.5, LI 4, ST 44
Temporal	Gall bladder Channel of foot-Shaoyang.	GB 8, TE 5, GB 41
Parietal	Liver Channel of foot-Yueyin.	CV 20, SI 3, BL 67, LR 3

lower limbs meet. Attacks by trauma and other endogenous or exogenous factors may cause derangement of *qi* and blood in the head and retardation of circulation of *qi* in the channels that traverse the head. In such cases, headaches occur. Usually, the headache is differentiated according to its locality and its supplying channels (Table 56-5). The selection of acupuncture points is based on the combination of local points around the symptomatic area and distal points according to the channels affected. Pain at the occipital region and nape of the neck is believed to be Urinary Bladder Channel of Foot – Taiyang related. Fengchi (GB 20) and Tianzhu (BL 10) are the local points punctured. Kunlun (BL 60) is one of the distal points selected often. Pain at the forehead and supraorbital region is related to the Stomach Channel of foot-Yangming. Puncturing the local points of Touwei (ST 8) and Yintang (GV 24.5) combined with distal points Hegu (LI 4), Neiting (ST 44) is one of the popular methods. Headaches at the temporal region bilaterally or only one side are related to the Gall bladder Channel of foot-Shaoyang. Shauigu (GB 8), Waiguan (TE 5), and Zulinqi (GB 41) are the points to be punctured. Parietal region headache is related to the Liver Channel of foot-Yueyin. The points often selected include Baihui (CV 20), Houxi (SI 3), Zhiyin (BL 67), and Taichong (LR 3). For those with exuberance of liver-*yang*, add Xingjian. (LR 2) and Yanglingquan (GB 34). In cases of deficiency of *qi* and blood Qihai (CV 6) and Zusanli (ST 36) would be punctured also.

Post TBI cases are differentiated to Shi (solid) and Xu (insufficiency) types. Cases with symptoms of stasis of blood and exuberance of liver-*yang* belong to Shi types, while those with symptoms of insufficiency of *qi*, blood and kidney are grouped as Xu types. The acupuncture points are selected accordingly. For example, Laogong, (PC 8) and Yongquan (KI 1) are the points to be stimulated for Shi cases with syncope and dizziness. However, combining puncture and moxibustion at Baihui (GV 20),

Qihai (CV 6), and Zusanli (ST 36) is the treatment for those Xu cases with similar symptoms.

More and more evidence supports that acupuncture is able to stimulate the central nervous system to release chemicals, which influence the body's self-regulating systems and promote natural healing abilities. Most acupuncture points are located in the trunk and limbs. However, the points over the head play an important place in traditional TBI management with acupuncture. Scalp acupuncture is a newly developed promising method to treat severe TBI and its related symptoms (46–48). Future research may be aimed at scalp acupuncture and its effects on the release of neurotransmitters and neurohormones.

## Discussion

Unlike the development of Western medicine, which is mainly based on the progress of biomedical sciences, the development of Traditional Chinese Medicine is based on the experience of numerous clinical applications of natural products and acupuncture. TCM has been used for at least 3,000 years and has accumulated rich clinical application experience. The chemical ingredients of natural products are complicated. The chemical contents of a TCM formula, made up of a combination of natural medicines, are even more complicated. Pharmacological research is needed to bring TCM from an experiential and historical level to current biopharmaceutical standards level. This is not to say that the chemical elements of TCM formulas should be extracted and purified into a single compound for administration in isolation.

Although there are increasing numbers of patients and physicians in western countries accepting TCM as an alternative form of medical treatment, there have been no large-scale, well-controlled studies done evaluating TCM management of TBI. Some “natural” ingredients may be harmful to humans. The issues of toxicity may be even more relevant following TBI when blood brain barrier permeability may be adversely impacted. Considering the complex contents of TCM medicines, it is certainly possible that some of them may interfere with the effects of prescribed pharmaceutical drugs. Most of the TCM medications mentioned in this chapter are available in the West as “natural food products”. The authors recommend that patients who wish to use TCM medications for TBI related problems consult their physicians, and if such treatment is pursued, patients should ideally be under the guidance of TCM trained practitioners.

Acupuncture seems to have no obvious side effects; however, there are no large-scale controlled studies done yet on acupuncture management of TBI related problems. Clearly, this is an area of research that can meld TCM with Western medicine in an attempt to best optimize patient outcome following TBI.

How ultimately TCM will be integrated into the rehabilitative management of persons with traumatic brain injury is yet to be seen. Practitioners should remain open to treatment strategies such as TCM that potentially assist their patients' recovery and/or function and commensurately advocate for these areas of intervention to be more critically assessed through high quality controlled research studies.

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# 57

## Complementary and Alternative Medicine

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**I**n the mid-1800's, medical and health care in the United States included a rich mixture of many different health care practices and philosophies from various cultures around the world. The introduction of the research control trial (RCT) and development of the scientific methodology and rigor which allowed for the proof of the efficiency of an intervention resulted in an explosion of effective medical treatments in the latter part of the nineteenth century. This successful biomedical approach continues to dominate the practice of medicine in western societies today. Traditional practices, although based on thousands of years of human experience, are now considered “complementary” or “alternative” therapies. Despite the predominance of the modern biomedical approach to medical practices the use of complementary and alternative medical practitioners in the United States and other Western societies continues to grow. Patients with brain injury may be particularly likely to seek treatment through CAM practitioners especially when there is a lack of effective treatment for many chronic impairments and symptoms associated with brain injury. The development of the research infrastructure, including centers of study and evidence-based scientific exploration has resulted in a growing body of literature related to the practices of CAM.

The purpose of this chapter is to explore the evolution of the modern biomedical approach to medicine from

traditional to the scientific. We discuss the application and implications of the growing consumer use of CAM as it pertains to our current medical and rehabilitation management of patients with brain injury. We contend that CAM interventions can be most appropriately and successfully integrated into rehabilitation management of brain injury with the development of the scientific evidence to support such practices. We also discuss CAM interventions which may be of special interest to patients with brain injury along with the availability and accessible research literature relative to the integration of CAM into evidence-based practice.

Complementary and alternative therapy (CAM) is defined as the use and practice of therapies or diagnostic techniques that are not part of the current Western health care system. It was not until the latter part of the nineteenth century that the scientific research and rigor which forms the foundation of the modern biomedical approach to medical practice was introduced. With the success and preferential development and emphasis on the biomedical approach, traditional practices, often based on thousands of years of human experience may have been inadvertently left behind. Consider for example Ayurveda, practiced throughout the Indian subcontinent for more than 7000 years. Ayurveda promotes (1) an integrated approach to the prevention and treatment of disease with a healthy lifestyle of diet, herbs, exercise and yoga. Another of Asia's contributions to alternative medicine

is Bencao Gangmu which was published during the Ming dynasty in China (1552–1558) (1). This text, by Li Shi-Zhen, lists 1,892 medical substances and contains more than 1,000 illustrations and 10,000 detailed descriptions. Chinese knowledge of botanic medicine dates back to 3,000 years B.C. with the discovery of Ma Huang, used as a stimulant and for respiratory afflictions. The active ingredient in Ma Huang was subsequently identified as ephedrine (1).

The modern biomedical approach to medical practice is based on an understanding of the pathophysiology of disease and scientific proof of the efficacy of an intervention. Some believe that this approach to medicine was established in the 2nd century AD by Galen, a Greek physician (1). Galen published a guide to the evaluation and treatment of patients which focused on anatomical knowledge and the use of visual and physical objectivity (1). In the 1800's, scholars in China also sought to move away from speculation and root their studies in "hard facts" (2) by practicing "Kaozhang" translated "practicing evidential research."

A landmark in the evolution of evidential research was the development of the randomized controlled trial. When James Lind (1716–1794) (3) was appointed as a ship's surgeon in Britain, scurvy was a crippling and prevalent disease among sailors. In his meticulous observations Lind included a simple account of what may have been the first prospective randomized controlled trial (RCT) ever undertaken in humans. With their full cooperation, Lind randomized sailors afflicted with scurvy into separate groups, each group receiving a different mode of treatment thought efficacious at that time. The results of the experiment were simply stated, "of the two men who had received 2 oranges and 1 lemon daily, one was fit for duty at the end of 6 days and one recovered to the point of attending the rest of the sick patients in the other groups". With this one concise clinical experiment Lind established the clear superiority of citrus fruits above all other supposed antiscorbotic remedies. Lind's work ultimately led to a government ordinance requiring the provision of citrus fruits to all sailors which in turn led to virtual eradication of this disease. Subsequently the continued systematic development of the scientific rigor which was so successful in proving the efficacy of interventions resulted in an explosion of effective preventative, diagnostic and therapeutic interventions. In medical education a report by Abraham Flexner early in the 20th century ultimately led to the disproportionate funding and development of medical schools which trained their students in the biomedical approach.

Despite the success and preferential development of the biomedical approach, patients in the United States and other Western societies are seeking treatment from traditional and alternative medical practitioners in growing numbers. Eisenberg et al. (4) performed a survey which

documented the expanding use of CAM interventions by American Families. This survey identified an increase in the use of CAM from 33.8% of families in 1990 to 42.1% in 1997 (4). Extrapolating from the survey results the author's suggested a 47.3% increase in visits to alternative medicine practitioners, 427 million in 1990 to 629 million visits in 1997. Visits to alternative practitioners exceeded total visits to all U.S. primary care physicians with estimated expenditures for alternative medicine services in at \$21.2 billion. CAM therapies were sought both for the maintenance of health and the prevention and treatment of illness. For conditions most pertinent to brain injury CAM interventions were sought for headache, neck problems, insomnia, depression and anxiety. An estimated 15 million adults in 1997 took prescription medications concurrently with herbal remedies and high dose megavitamins and less than 40% of patients disclosed this to their physicians (4).

Physicians attitude towards CAM was evaluated in a survey in 1997 by Sikand et al. (5). This survey was mailed to the fellows of the Michigan Chapter of the American Academy of Pediatrics (5). The majority of pediatricians responding believed a small percentage of their patients were seeking alternatives to conventional medicine. In addition, half of the physicians responding would consider referring patients for CAM, and most were interested in continuing medical education on CAM (5). In 1999 Spencer et al. reported that 63 US medical schools were offering courses and electives in CAM(6) however CAM therapies remained largely outside of most conventional medical school curriculums. The increasing use of CAM led to an awareness of the need for further research into CAM and may have prompted Congress to establish the Office of Alternative Medicine (OAM) at the National Institute of Health (6). Funds were appropriated to establish 11 centers of study and with the development of these centers the literature devoted to CAM has expanded and the number of research CAM databases has grown (6). Subsequently the World Health Organization designated the OAM as a collaborating center for traditional medicine (6).

There are inherent differences in the biomedical and CAM approach to medical practice. CAM interventions are often based on a philosophy and a holistic approach and often rely on verbal reports to evaluate effectiveness. Recognizing these fundamental differences Katz et al. (7) proposed a method of evidence mapping to evaluate the strength of the evidence in CAM. Evidence mapping systematically organizes the evidence available pertaining to a broad topic such as CAM. The breadth, depth, methodology and overall quality of pertinent evidence are characterized. Evidence mapping seeks to be broadly inclusive, performs abstractions and detailed assessments including systematic reviews and meta-analysis. The study objectives included, mapping the evidence underlying

CAM, identifying high priority areas of deficient evidence and conducting pilot studies in the areas where evidence is sparse. With this method of evidence mapping Katz et al. identified over 4,000 papers distributed to over 207 priority health care areas. Of conditions most pertinent to BI Katz et al. identified 7 RCT's relating to the use of CAM interventions in headache and 15 for the use of CAM in neck pain. Depression was considered one of the top 25 priority health care areas and 11 RCT were devoted to the study of relaxation and depression. There were a total of 112 studies in the use of vitamins and depression of which 41 were RCT. Fatigue was also included in the top 25 priority health care areas and 2 RCT were identified in the use of herbs for fatigue.

In a method similar to evidence mapping, consensus conferences draw from a broad body of experts to evaluate the evidence of therapeutic interventions, for example the NIH and the OAM sponsored a consensus conference evaluating the quality of research assessing the efficacy of acupuncture, unfortunately this conference concluded that generally the quality of the evidence was low with few well-designed studies assessing efficacy of acupuncture (8).

The development of research centers and internet access to electronic research databases set the stage for Gordan Guyatt at McMaster University in Canada to propose a paradigm shift in health care called evidence based medicine (EBM) (9). EBM is defined as the integration of best research evidence with clinical expertise and patient values. The agency for health care policy research (AHCPR) has sponsored several programs closely identified with evidence-based medicine in the United States (10). The Medical Treatment Effectiveness Program funds research on the efficacy, cost effectiveness, and appropriateness of clinical interventions. The AHCPR supports 12 Evidence Based Practice Centers, which include a mixture of academic centers and private organizations with national and international reputations for their work on systematic reviews, meta-analyses, and technology assessments. Several centers are devoted to complementary and alternative medicine including the following: Center for Alternative Medicine Research in Asthma and Immunology at the University of California at Davis; Center for Addiction and Alternative Medicine Research at the University of Minnesota; Complementary and Alternative medicine program in aging at Stanford University (10).

The Cochrane collaboration uses an evidence based approach including a registry of randomized control trials and systematic reviews. Systematic reviews critically appraise the qualitative aspects of the research literature and the strength of the evidence to support a particular intervention. Within the Cochrane database there is a complementary therapy research section. The Database of Abstracts of Reviews of Effectiveness (DARE) (11) published, in 2003, a systematic review of randomized

control trials of complementary/alternative therapies in the treatment of tension-type and cervicogenic headache. Two reviewers used an 18-item quality protocol for adult headache sufferers. The participants in most studies were patients with tension type headache. A minority of patients suffered from cervicogenic or post-traumatic headache. Of the studies, which received a high quality, 1 RCT on the use of homeotherapy in 98 patients found no difference in efficacy of the treatments provided. One Research controlled trial (RCT) including 57 subjects found that Tiger Balm and paracetamol produced significantly greater pain relief for one episode of headache.

EBM has now been incorporated throughout health care curriculums and for clinicians trained in the biomedical approach, evidence based medicine is the safest and most effective means of incorporating the research available in complementary and alternative medicine into conventional clinical practice. EBM stresses the need for the clinician to examine the available information, or lack of information, from clinical research and to critically analyze the literature and incorporate the results of such analysis into clinical practice including the use of CAM. The expansion in the availability of health sciences electronic databases and libraries has supported the access and availability of pertinent research on CAM in real time to clinicians. The OAM, the creation of specialized centers and databases of systematic reviews of best evidence allows clinicians rapid access to concise summaries and evaluations of the evidence to support the therapeutic and diagnostic practices of CAM. See (Table 57-1) for electronic databases which contain literature applicable to CAM.

In the following sections of this chapter we explore some of the CAM techniques in common use in the US from a historical and traditional perspective, as well as the available research evidence to support the CAM practice especially as applicable to patients with brain injury.

## HOMEOPATHY AND NATUROPATHY

Homeopathy is a 200-year-old therapeutic system that uses small doses of various substances to stimulate self-regulating and self-healing processes (12). Of the nearly 2.5 million patients using CAM in the United States in 1997 approximately 3.4% of patients used homeopathy and 0.7 % used naturopathy (13). Homeopathy remains one of the most controversial CAM's. *Similia similibus curentur* or, treating "like with like" is the basis of homeopathy. Homeopaths believe that patients complaining of particular symptoms can be cured with substances that can produce the same symptoms in healthy individuals. In addition to matching the symptoms of the disease, a homeopathist will select remedies based on the constitutional factors of the individual patient such as the patients' psychological state, environmental reactions, and habitus. Of the large number



**TABLE 57-1**  
**Evidence Based Databases and CAM**

- The Cochrane Library: <http://www.cochrane.org/index0.htm>
  - Cochrane Central Register of Controlled Trials:
  - Cochrane Database of Systematic Reviews:
  - The Database of Abstracts of Reviews of Effects (DARE)

Published by Wiley InterScience with new and updated Cochrane Reviews every three months.
- ACP Journal Club <http://www.acpjc.org/>.
- InfoPOEMS/InfoRetriever (<http://www.infopoems.com/>)
- PubMed (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi> searchers can apply the limit “Complementary Medicine”\*\*)
- Bandolier <http://www.jr2.ox.ac.uk/bandolier/booth/booths/altmed.html> \*\*
- MD Consult-First Consult (<http://www.mdconsult.com/offers/standard.html>).
- EMBASE (<http://www.embase.com/>).
  - Alt HealthWatch (via EBSCOhost). <http://www.epnet.com/academic/althw.asp> MANTIS (see <http://www.healthindex.com/MANTISDatabaseOverview.html>) Natural Standard (see <http://www.naturalstandard.com/>)
- The TRIP Database (see <http://www.tripdatabase.com/>)
- AMED – Allied and Complementary Medicine Database (produced by the Health Care Information Service of the British Library) <http://www.bl.uk/collections/health/amed.html#net>
- Herbal database <http://www.herbmed.org/>: an interactive, electronic herbal database – provides hyperlinked access to the scientific data underlying the use of herbs for health. Evidence-based information resource provided by the nonprofit Alternative Medicine Foundation, Inc.

\*\* available without subscription.

of homeopathic medicines which have been described, approximately 200 are in regular use (14) and about 60% of plant origin. Animal products, minerals, chemical salts, and disease products also may be used. Homeopaths believe that remedies retain biological activity if they are serially diluted and agitated between each dilution. The dilution most frequently used is designated “6c”, which is a  $10^{-12}$  dilution of the original “mother tincture”. It is likely that a 6c dilution will contain a few molecules of the initial substance. These dilutions are said to produce effects even when diluted beyond Avogadro’s number in which no original molecules of the starting substance remain. Many scientists believe that homeopathy violates natural laws and thus any effect must be a placebo effect (15). However, because of the high dilution, homeopathy appears to be very safe, which is an important motivating factor amongst its patients. The public’s belief in the effectiveness of homeopathy is widespread (16). In the United States, patients who seek homeopathic care are more affluent and younger (17). As with other diseases and syndromes, the effectiveness of homeopathy for brain injury (BI) is quite questionable and controversial. A small pilot research study suggested that homeopathy is efficacious for certain symptoms related to brain injury such as headache (18, 19). Actually, there is insufficient evidence to show that homeopathy is clearly efficacious for any single clinical condition. Reviews on homeopathic clinical trials have found that the majority of available studies have

reported some positive results but the evidence is not convincing (20, 21).

There is no concise history of naturopathic medicine since the development of naturopathy has been strongly influenced by various cultures and religions and is therefore not a single discipline. Naturopathy and conventional medicine hold certain principles in common. Both emphasize disease prevention, patient education, seeking and treating the causes of disease, and both employ the therapeutic potential of the doctor-patient relationship. The basic principle of naturopathy dictates that nature acts powerfully through healing mechanisms in the body and mind to maintain and restore health. Naturopaths work to restore and support these inherent healing systems using non-invasive treatments believed to be in harmony with natural processes such as lifestyle modifications, nutrition, dietetics, herbs, education, and hydrotherapy. In addition, naturopaths may elect to use a variety of healing modalities including acupuncture, botanicals, homeopathy, massage, oriental medicine, and minor surgery (22). In general, naturopaths function as primary care providers with emphasis on prevention, education, and health maintenance (23, 24). It is vital that naturopathy be incorporated into conventional medical practices where treatment which has been proven to be effective is available, for example if a BI patient develops progressive hydrocephalus, a neurosurgical procedure may be appropriate to prevent further neural damage and facilitate

functional recovery. It would not be appropriate to over-emphasize natural healing and natural treatment modalities in such situations.

Most of the modalities applied by naturopathy are relatively safe, however, they are not without any risks (25, 26). Naturopathy recommends administering vitamins and herbal medicines widely, even though more clinical trials are necessary to obtain evidence supporting their efficacy. For example, vitamins A, C, and E are considered necessary for protecting tissue free radical damage and are commonly used by naturopaths, however, there is not enough scientific data supporting their necessity in addition to what is consumed in a normal diet (27). Only a small fraction of the thousands of medicinal plants used worldwide have been tested rigorously in randomized controlled trials (28). Several clinical trials have shown that some herbal or natural medicines may have efficacy in BI related symptoms, for instance, use of hypericum perforatum (St. John's wort) for depression and Ginkgo biloba for dementia is supported by a significant amount of evidence (29–31). Results of randomized controlled trials also support the use of kava for anxiety and valerian for insomnia (32, 33). Although evidence for the use of vitamins and amino acids as sole agents for BI related neuropsychological symptoms is not strong, there is intriguing preliminary evidence for the use of folate, tryptophan, and phenylalanine as adjuncts to enhance the effectiveness of conventional antidepressants. Another product S-denosylmethionine seems to have some antidepressant effects, while omega-3 polyunsaturated fatty acids, particularly docosahexaenoic acid, may have mood-stabilizing effects (34). It is important to note that scientific evidence is still lacking to support that the natural methods serve any therapeutic purpose better than conventional management. The scientific evidence is also lacking regarding what kind of natural foods the body can use for "reconstruction". Rehabilitation physicians should ask their BI patients about the "natural products" they take and discuss their use in a frank and nonjudgmental manner. The potential side effects and drug-drug interactions should also be considered when initiating naturopathy (35, 36). Patients who seek alternative medical management may do so because the available standard pharmacological treatments are not effective for their symptoms however the evidence on the effectiveness of homeopathy for post BI patient is scant. Some of the natural herbs may have effects to relieve some BI related symptoms; however, there is inadequate evidence to support the natural methods as serving the therapeutic purposes better than conventional. Natural herbs also have potential side effects and may induce drug-herb reactions. Rehabilitation physicians should maintain open communication with their patients to help them understand the potential, sometimes adverse drug-herb interactions and to ensure patients are informed of effective therapies for

serious diseases when the evidence for effective conventional therapy exists.

## AROMATHERAPY

Aromatherapy is the therapeutic use of aroma-producing oils (essential oils) extracted from organic materials (flowers, leaves, stalks, bark, rind or roots), and utilized as a form of relaxation therapy. The oils are mixed with another substance such as an alcohol, oil, or a lotion, and are then applied to the skin, sprayed in the air, or inhaled. The oils can also be poured into a soaking bath to derive the therapeutic effect. Originating in Europe in the early 1900's, the philosophy behind aroma therapy is that specific plant oils produce aromas and fragrances that stimulate or relax the body, by acting on certain areas within the brain. Fragrances stimulate nasal nerves which then send impulses to the areas of the brain controlling memory and emotion. The oils themselves are thought to interact with the body's own naturally occurring hormones and enzymes to cause changes within autonomically-mediated reflexes, including the blood pressure and pulse. Theory suggests a fragrance stimulates glands to produce analgesic substances, perhaps prostaglandin stimulating substances, effecting relaxation pain relief. Practitioners utilize essential oils to treat physical conditions including inflammation and infection. Aroma therapy is used to treat mental health conditions, including anxiety, depression, and insomnia. Individuals with asthma, respiratory allergies, chronic lung disease, or certain skin allergies should use care participating in aromatherapy. Aromatherapy should be avoided in children under the age of five as their immune systems are not yet competent.

## RELAXATION THERAPIES

Meditation is a relaxation therapy where one's attention is directed toward altering one's own state of consciousness. Meditation is a complex mental process involving changes in cognition, sensory perception, affect, hormones, and autonomic activity (37). The health benefits of meditation have been recognized in eastern philosophies for thousands of years with meditation now widely practiced in the west. There are two meditation techniques most commonly used: concentrative and mindful. In concentrative meditation, one focuses on a single image, sound, mantra (words spoken or sung in a pattern), or one's own breathing. Mindful meditation does not focus on a single purpose; rather, one is aware of all thoughts, feelings, sounds or images that pass through one's mind. Meditation usually involves slow regular breathing and quiet sitting, usually for durations of fifteen to twenty minutes. Meditation is used to help treat

a wide range of physical and mental problems, including addictive behaviors; immune system diseases; anxiety, stress, depression; high cholesterol and high blood pressure; and, pain. There are believed to be no negative side effects or medical complications of meditation when combined with conventional medical treatment. Meditation alone is not considered appropriate or safe for acute or life-threatening situations.

Transcendental meditation (TM) is unique and fundamentally different from any other type of meditation. It was founded by the Maharishi Mahesh Yogi in 1957. TM is reportedly a very simple technique to learn and is simple to practice. Over 5 million people around the world, almost 200,000 in the United Kingdom, have learned the technique since it was founded in 1957. People learn TM for many reasons, including reducing stress, improving health, and increasing personal effectiveness. The first scientific research on TM was published in 1970, and now there are hundreds of published studies documenting the benefits for mind-body relationships and the environment. TM is neither mind control nor mental discipline. It is not concentration, eastern philosophy, or a way of life, and it does not exert control over breathing or muscles. Hypnosis is a state of focused concentration during which time a person becomes less aware of their immediate surroundings. The use of hypnosis and hypnotherapy have been recognized by the American Medical Association as a valid medical treatment since 1958. Hypnotherapy has been used to treat many physical or psychological conditions, and can be led by a therapist, or it can be taught to individuals, for self-hypnosis. It is thought that during hypnosis, a trancelike state, individuals have a heightened ability to accept suggestions. By suggesting changes in an individual's actions or behavior, an improved physical or mental condition is created. The hypnotherapist's goal is not to control a person, or give the person answers, but rather to help the person solve his or her own problems. Hypnosis does not work for everyone, as a person must be willing to directly focus his or her attention and follow the suggestions of the therapist. Hypnosis is covered in greater detail in another section of this chapter; but it is mentioned here as it is considered a powerful relaxation and self-improvement therapy (38).

Guided Imagery is a relaxation technique where a series of thoughts or suggestions direct a person's imagination toward a relaxed and focused state. An instructor, in person or on recorded media, guides the individual through the process of imagery. Guided imagery is based on the concept that one's mind and body share a unique connection. Using the special senses, one's body seems to respond as though what one is imagining is, indeed, occurring. A relaxed state may be achieved when it is imagined, in full detail. This relaxed state can then aid learning, healing, and performing. Guided imagery can

have one feeling in control of one's emotions and thought processes, which then improves one's attitudes, health, and well-being. Guided imagery is especially useful in promoting relaxation. This relaxed state can lower blood pressure; reduce other stress-related problems, and enables one to reach other goals. Guided imagery is helpful in preparing for athletic events and for performance enhancement, including learning, weight loss, smoking cessation, and pain management. Guided imagery is safe, with no known associated risks, and it can be performed in any circumstance where improved performance is desired.

Autogenic training is a relaxation technique that teaches your body to respond to your own verbal commands. Using certain commands, a practitioner of autogenic training is able to tell their own body to relax, thus controlling breathing, blood pressure, heart rate and temperature. Autogenic training consists of six standard exercises that enable the body to feel relaxed, heavy, and warm. Each exercise has the individual assuming a simple posture, concentrating without goal, and then using visual imagery and verbal cluing to promote relaxation of the body in a specific way. The ultimate goal of autogenic training is to allow the individual to achieve a deep relaxation and stress reduction. Autogenic training is an effective treatment for chronic stress, as well as for other mental and emotional health issues. The mechanism of action is not fully understood, but the effects on the body are measurable. Experts believe that autogenic training works similarly to hypnosis, or self-hypnosis, or biofeedback. Helpful, with problems like generalized anxiety, fatigue, and irritability, some use autogenic training to manage pain, reduce sleep disorders, or increase their resistance to stress. Autogenic training has shown effectiveness in addressing: hyperventilation, asthma, gastrointestinal disorders, cardiovascular irregularities, autonomic dysfunction, headaches, and endocrine disorders. Some individuals have noticed a sharp change in their blood pressure when practicing autogenic training exercises; therefore, it is recommended that individuals with hypotension or hypertension have their individual physician's approval prior to participating in autogenic training. Autogenic training is not recommended for children under the age of five or in individuals with severe mental or emotional disorders (39).

Humor therapy, occasionally known as therapeutic humor, is a relaxation method that uses the power of smiles and laughter to help heal. Therapeutic humor, or humor therapy, simply means finding ways to make others, or yourself, smile and laugh more often. Laughter appears to actually change the brain chemistry, demonstrated on P.E.T. scans, and it may also boost the immune system, as well. Humor allows people to feel in greater control of their situations, can provide special perspective on problems, can allow the release of fear and anger, and it can eliminate stress that can create harm. Commonly,

humor is used in the treatment of long-term and chronic diseases, especially those worsened by stress. Humor therapy is valuable as well as a preventative measure aiding the care-partners of people with chronic illness or disease, including stroke, heart attack and brain injury, as they are at high risk of becoming ill themselves.

Music therapy is a relaxation therapy used to promote physical and emotional healing and wellness. Generally, a trained and certified music therapist is able to offer therapy in school, healthcare facility, hospice mental health facility, and private practice setting. Sessions of therapy can involve passive listening, active music making, or both. Research is currently revealing how music works therapeutically on both body and mind. The rhythm and tone of music can stimulate or sedate; has positive effects on heart rate, oxygen saturation, blood pressure, and cognitive ability; and is a healthy, non-verbal mode of self-expression. It is socially connective and expressive; and it enhances verbal expression, fluency, and communication with self and with other individuals. Music therapy calms the body and mind, and with its rhythm, order and function, it organizes the mind. Sometimes, music therapy, combined with movement therapy, such as dance, is utilized as a combined therapy. Long-term and medium term memories appear stimulated with music therapy and it has been shown that newborn premature infants, in intensive care units, are better able to tolerate painful procedures when exposed to music therapy. There are no known risks to music therapy and more information can be obtained by visiting the American Music Therapy Association website at [www.musictherapy.org](http://www.musictherapy.org) (40).

Biofeedback is a relaxation therapy where an individual, utilizing physical and mental exercises, consciously seeks to control a bodily function in a manner normally autonomically regulated. The bodily function (under control) is measured and displayed on monitors, concurrent with the treatment, demonstrating the individual's self-control. Once an individual achieves the desired functional change, monitors flash lights or sound audible signals. Biofeedback is of two types. One device uses electromyography (EMG) as the principal device for measuring relaxation; the other device uses peripheral limb temperature for feedback. Learning biofeedback routinely requires multiple instructor-led sessions to achieve competence. Beyond relaxation, electroencephalographic (EEG) biofeedback has become a widely used alternative treatment for a variety of neurologic and non-neurologic conditions.

## ELECTROENCEPHALOGRAPHIC BIOFEEDBACK

EEG biofeedback (also known as neurofeedback or neurotherapy) is a widely used alternative treatment for variety of neurologic and in-neurologic and non-neurologic conditions. Based on the same principles as conventional

(somatic) biofeedback. EEG biofeedback teaches individuals to modify, through the use of computerized feedback, the electrical activity of their own brains (41). As in other biofeedback modalities, the goal is to make normally unconscious or involuntary bodily processes perceptible so that they can be manipulated consciously. In conventional biofeedback, targets include such somatic processes as muscle tension, heart rate, and skin temperature. In EEG biofeedback, on the other hand, the target processes are certain characteristics of the patient's own EEG, such as frequency, amplitude, or cerebral localization.

During a typical EEG biofeedback session, the patient's brainwaves are recorded through scalp electrodes placed according to the "10-20" system used in traditional EEG recordings. The raw signal is amplified, filtered, and analyzed by specialized software which determines by how much the patient's EEG pattern deviates from target values that are determined ahead of time by the treating clinician. This information, in simplified form, is then communicated to the patient ("feedback"). Usually, the patient is only informed as to whether or not they are reaching their targets. This feedback can be delivered by something as simple as a light or sound that turns on only when patients are in the target range. Newer systems are characterized by more sophisticated and engaging modes of delivering feedback. For instance, one system utilizes a "Pacman" style video game: the "Pacman" character only moves (and thus scores points) when the EEG pattern is in target range. The costs of an EEG biofeedback session can range from \$50 to \$150 per session and most practitioners recommend an average of 40 (range 20-60) sessions for TBI, resulting in a total average cost of approximately four thousand dollars for a full course of treatment.

There are few, if any, dangerous side effects reported, although practitioners express concern about the possibility of triggering a seizure in patients with a known seizure disorder (this despite the fact that EEG biofeedback is considered a treatment for epilepsy). In general, the reported side effects already assume that EEG biofeedback is efficacious. For instance, practitioners will report concerns about "overshooting" and agitating a person with reduced initiation. Or, conversely, causing someone who is restless and anxious to become too sedated. Obviously, whether or not these side effects actually occur depends on whether EEG biofeedback can actually modify neurological or psychological symptoms.

The proposed mechanism of action of EEG biofeedback rests on two assumptions. First, it is assumed that EEG patterns are correlated with neurological or psychological states. For instance, the EEG of someone with anxiety disorder is thought to differ in predictable ways from the EEG of someone with depression. There is a fair degree of empirical support for this claim (42-44). There is also evidence for the second assumption, namely that

individuals can be trained to modify features of their own EEG (45). Thus, one proposed explanation of how EEG biofeedback works is that patients are learning to “normalize” abnormal EEG patterns and that, as these patterns are normalized, the patient’s symptoms improve or even resolve completely. Despite the empirical support for the assumptions that underlie this explanation, there is only limited evidence for the efficacy of EEG biofeedback in ameliorating clinical symptoms.

The FDA does not regulate either EEG biofeedback as a treatment modality or the equipment used (except generically as general biofeedback equipment). In addition, there are no local or national standards regulating the training or qualifications of those who provide this treatment. There are two national competency certifications offered by the Biofeedback Certification Institute of America as well as the Neurotherapy and Biofeedback Certification Board; however, these are strictly voluntary. Although anyone can provide these treatments, most providers tend to be professionals licensed in the fields of psychology, medicine, counseling, etc. It is estimated that approximately 3000 clinicians are currently providing EEG biofeedback treatment in the U.S. (46).

In fact, EEG biofeedback has been used for approximately 30 years to treat a variety of psychological conditions (including attention deficit disorders, depression, substance abuse, etc.) (47–52). There is a professional society entirely devoted to EEG biofeedback (International Society for Neuronal Regulation, with approximately 400 members) as well as an EEG Biofeedback Section (with approximately 600 members) in the well established Association for Applied Psychophysiology and Biofeedback. There are textbooks (53, 54) and a professional journal (*Journal of Neurotherapy*) devoted to the field. In addition, there are a growing number of dissertations being written on the topic. Finally, EEG biofeedback has become increasingly visible amongst consumers with TBI and their families. Recently, the Brain Injury Association of America published an article that discussed the modality in their national magazine (55). In addition, the state of Texas passed a law in 2001 mandating that commercial insurers must cover EEG biofeedback services for individuals with TBI (56).

The earliest and strongest evidence for the efficacy of EEG biofeedback is in the treatment of epilepsy. The intuition behind this research was the recognition that epilepsy was, by definition, a condition characterized by disordered electrophysiology. The goal was to teach individuals to modify those aspects of their EEG that most strongly correlated with seizure risk. Since 1972, there have been over 20 articles in peer-reviewed journals reporting on the use of EEG biofeedback to reduce seizure frequency in epilepsy; these have been recently summarized (57). Several of these articles reported the results of trials (including blinded, placebo controlled trials). The results were almost

uniformly positive and supported the efficacy of EEG biofeedback in reducing seizure frequency. Indeed, even a recent review article that was skeptical of EEG biofeedback acknowledged its potential role in epilepsy (58).

Unfortunately, as noted by the same reviewer, the evidence of efficacy in the treatment of other neurological or psychological conditions is much more limited. Much of it has been in the form of case reports and case series (59) which have been systematically reviewed in several recent articles (60–65). Recently, however, several trials evaluating the efficacy of EEG biofeedback for attention deficit disorder (66–69), learning disabilities (70, 71), anxiety disorders (72–74), substance abuse (75), and fibromyalgia (76) have been published and all of them supported the efficacy of EEG biofeedback. Unfortunately, these studies all had significant methodological weaknesses that limit the conclusions that can be drawn from them. These weaknesses include: high risk of Type I error due to multiple outcomes and multiple statistical comparisons, small sample sizes, lack of blinded assessments, and lack of adequate controls (including the lack of blinded control groups) (77, 78). Recognizing these methodological flaws the two primary organizations in the field recently assembled a task force on “Methodology and Empirically Supported Treatments” which discussed some of the methodological problems unique to the field of EEG biofeedback (in contrast, for instance, to pharmaceutical research). These authors published a set of standards (79). These recommendations have been echoed by others (80).

With regards to TBI, the published literature is even more sparse. Here, too, all of the published accounts reported positive results. However, the number of articles in the peer-reviewed literature is very small and consists primarily of case reports (81) and case series (82–85) although two prospective trials (86, 87) have recently been published. Moreover, the published reports have almost exclusively involved individuals with mild TBI (88). There have been no published reports on individuals with primarily moderate or severe TBI.

The best designed prospective trial in TBI (89) still shares many of the methodological weaknesses of the studies discussed earlier. In this NIH funded study, 12 subjects with chronic, symptomatic, predominantly mild TBI were randomized into either an active treatment group or a wait-list control group. The treatment consisted of 25 sessions of neurotherapy over 8 weeks. Outcome measures, comprised of symptom rating scales and neuropsychological tests, were administered at baseline, post-treatment, and at three-month follow-up. Once the initial active treatment group finished treatment, the wait-list control underwent the same treatment protocol. At the conclusion of the study, two different types of statistical analyses were performed.

First, the results for the two different groups (active vs control) were compared in a “between-groups”

analysis. Subsequently, the results of all subjects were pooled and their pre- and post-treatment outcomes were compared in a “within-groups” analysis. The analyses revealed that subjects experienced improvement in a variety of different domains (8 out of 26 measures in the between-groups analysis and 18 out of 26 measures in the within-groups analysis). The authors concluded that “taken as a whole, the findings of this study are strong enough to identify Flexyx Neurotherapy System as a promising new treatment for TBI, which merits further evaluation” (89).

Despite the promising results, there are several limitations of this study. These include a very small sample size ( $n=12$ ), heterogeneous sample composition (9 mild and 3 moderate TBI), no mention of issues of subject retention/drop out, lack of a placebo control group, unblinded outcome assessments, no correction for practice effects seen in the neuropsychological measures, and multiple outcomes/statistical testing. The authors of the study recognized many of these weaknesses and correctly point out that many of them are inherent in the exploratory nature of the study. However, they are all issues that any future study must address.

In summary, there is insufficient evidence currently to support the use of EEG biofeedback in the treatment of TBI. However, the evidence of efficacy in other conditions is promising and more studies are clearly warranted. In the meantime, clinicians may choose to discuss this option with their patients, especially when there seem to be no further conventional treatments for relevant applicable symptoms. The relatively low risk and costs associated with EEG biofeedback make EEG biofeedback one of the more attractive options in alternative medicine. However, the clinician should stress the lack of research evidence supporting its use in TBI.

## ENERGY-BASED THERAPIES

Bi-Aura therapy is an energy-based therapy which works to seek out, and remove, energy blockages from within the body and from within the body’s energy field (aura or bio-field). Eastern medicine has long recognized the known energy and energy flow from the body, also known as Ch’I, Qi, and Prana. Bi-Aura therapy is a therapy in which a practitioner mostly through non-touch Bi-Aura techniques removes imbalances in the body’s energy field. These imbalances can occur from trauma, physical and emotional distress, and from physical illness. Bi-Aura therapy seeks to locate energy imbalances, address them, and allow the body to return to health. Bi-Aura therapy can also function to help balance the mental and emotional state of the individual by clearing these bio-field blockages and restoring health. Light therapy, known also as phototherapy, involves the exposure to bright, non-full spectrum light. White light is considered optimal over

narrow band wavelengths or ultraviolet light, both of which have been demonstrated to be toxic to skin and internal organs. It is believed that light therapy has an anti-depressant affect, that it may help balance certain brain chemicals, and that it may help reset proper circadian rhythms within the brain. Light therapy of 2,500 to 10,000 lux is generally considered safe and is considered one of the first lines of therapy for seasonal affective depression (SAD), a transient affective disorder affecting many during the cold and shortened daylight periods found in more northern latitudes, in the winter. The side effects of light therapy include visual disturbances with eyestrain, headaches, or skin irritation being the most common (90–92).

Healing touch therapy is an energy-based therapeutic approach to healing. Healing touch influences the energy system that is life itself. By assessing and treating the energy system, the practitioner helps the patient to self heal. Healing touch begins with the thought that people are naturally healthy, and that physical and emotional stress disturbs the natural energy, thereby causing illness. The goal in Healing touch is to restore wholeness through harmony and balance, through the “centered heart”. It is non-invasive and economical (93). Healing touch is not considered appropriate or safe for acute life-threatening situations.

Reflexology is a type of energy-based therapy that predates the discovery of the new world. Reflexology presumes that there are specific areas in the hands and the feet, reflex points, that correlate to analogous organ systems in the body. Manipulation of these reflex points is believed to promote mental and physical relaxation-relaxation that then promotes healing. Reflexology is used to treat one of nine principle systems, each representing a major organ system, thereby aligning the harmony of the body. The results of reflexology have reportedly been most impressive in treating musculoskeletal disorders. Reiki is an ancient healing method that uses a hands-on approach to manipulate energy flows throughout the body. Reiki means “universal life energy and practitioners believe that there is an energy force in and around one’s body, flowing between the person performing Reiki and the receiver of the treatment. It is thought that Reiki releases your own energy flow and allows your body’s own natural healing ability to work. It is completely non-invasive, and the Reiki practitioner will put his or her hands over the body of the recipient at one of the main energy centers, called chakras. Reiki is occasionally utilized to assist sufferers with chronic pain. Some health professionals believe it may be useful in helping to acutely reduce stress and anxiety, which in effect may help to facilitate the natural healing process.

Massage therapy has a long history with many different types developed over centuries. These vary from light touch to very deep massage. Some forms focus on

specific points or body areas. The many types and subtypes are beyond the scope of this chapter. Like other consumers of massage therapy, individuals with brain injury seek relief of pain and musculoskeletal symptoms using massage. Massage therapy has been successfully used in a number of post-traumatic pain syndromes as well as chronic pain syndromes for patients both with and without brain injury. Massage therapy forms part of most physical therapy interventions for myofascial pain syndrome in conjunction with trigger point injections and stretching (94). Gam et al. (1998) (95) studied the long term effectiveness of massage, exercise, and ultrasound treatments for myofascial pain syndrome using a randomized controlled trial of 67 individuals. They found that exercise and massage, but not ultrasound, resulted in a decreased pain measured by visual analog scale and improved trigger point index scores when followed up six months later. In a survey of individuals with neck or back pain 54% used a complementary health care provider compared to 37% using a conventional provider. Of the 14% choosing massage, 65% found it "very helpful" compared to 27% receiving conventional care (96) (Wolsko 2003). Massage therapy has been shown to be effective in 2 randomized clinical trials as a treatment for chronic low back pain (97). Hernandez-Reif et al. (2001) (98) compared the effectiveness of relaxation therapy to massage therapy in 24 adults with nociceptive back pain of at least 6 months duration or longer. Patients were randomized to either relaxation therapy or 30 minutes of massage twice weekly for 5 weeks. Those individuals receiving massage had less pain, better sleep and higher dopamine and serotonin levels. A meta-analysis of randomized or quasi-randomized research trials for individuals with chronic or subacute low back pain suggests that massage may be effective for pain relief especially when exercise and education are also included in the treatment plan (99). Massage has been applied to temporomandibular joint dysfunction (TMD). In a survey of complementary and alternative therapy (CAM) use by individuals with TMD, CAM with massage was the most frequently used, the most satisfactory and the most helpful (100).

The literature specific to traumatic brain injury is less substantial. Post-traumatic headache has been shown to respond to cervical massage better than cold packs in one prospective clinically controlled study (101). A case report successfully used massage therapy for hypersexuality after traumatic brain injury (102). In other patient populations massage produces relaxation, decreases anxiety and decreases pain (103). Massage was rated highly in survey of spinal cord injury patients for pain control (104). One mechanism of action that could account for better pain control, decreased anxiety, and the induction of relaxation could be increased parasympathetic activity. Parasympathetic activity can be assessed by analysis of heart rate variability. The respiratory sinus arrhythmia

(the mild acceleration and deceleration of heart rate associated with breathing) has a parasympathetic component that can be isolated through analysis of heart rate variability. In a randomized controlled trial evaluating the short term autonomic effects of massage to the back, neck and shoulders on 30 healthy individuals, (105) noted significantly decreased systolic blood pressure and increased parasympathetic activity. Other possible mechanisms producing these effects could be soft tissue mobilization with passive stretching, stimulation of circulation to remove accumulated metabolic products in chronically tense muscles, and the effect of touch itself. In summary, the general literature supports the use of massage to reduce pain and anxiety in patients with post-traumatic pain syndromes such as neck and back pain, temporomandibular dysfunction, and myofascial pain syndrome. There is a smaller quantity of literature supporting its usefulness in other neurologic conditions such as spinal cord injury and stroke. Massage also forms an adjunct to other therapeutic interventions provided by physical therapists, occupational therapists, massage therapists and non-conventional body workers. The literature specific to brain injury is sparse, but for musculoskeletal post-traumatic pain syndromes may be generalized to brain injured individuals.

## CRANIOSACRAL MANIPULATION

William Garner Sutherland, DO, devised craniosacral manipulation, also known as osteopathy in the cranial field, starting in 1939. Craniosacral osteopathy is used by osteopathic physicians (DO), allopathic medical doctors (MD), and dentists who attend research conferences and clinical courses presented by the Sutherland Cranial Teaching Foundation and the Cranial Academy. An extensive research bibliography is available from the Cranial Academy (106). A derivation called CranioSacral Therapy has been developed by John Upledger, DO, for massage therapists and other allied professionals who train at the Upledger Institute. Most CST practitioners are exposed to only a simplified version of the method, and chiropractors practice another variation called SacroOccipital Therapy.

After observing a disarticulated skull, Sutherland noted that bone and suture relationships were "beveled like the gills of a fish, indicating respiration" (107). Because this inherent pulsatile movement begins with embryonic development, well before the neonate's first breath of air, he called this phenomenon the Primary Respiratory Mechanism (PRM). The PRM provides the midline organization of structural and functional development. This impulse can be traced from the embryonic plate to the notochord, continuing in the adult as the oscillations between the lamina terminalis in the skull and the phylum terminale at the base of the spinal cord. In the

same way that one can take a pulse to assess heart rate and count breaths to determine respiratory rate, one can learn to palpate subtle motions of the skull that correlate clinically with central nervous system motility. Research has only recently corroborated the millimeter-scale movements of the cranial vault that Sutherland identified with his hands (108). Even a cadaver's cranial bones move when typical craniosacral pressure is applied (109). Normal physiologic movements of the cranial vault are described as cycles of flexion and extension, occurring approximately six to fourteen cycles per minute. Sutherland called this the Cranial Rhythmic Impulse (CRI). Restrictions and alternations of the CRI include patterns of torsion, strain, and compression involving the craniofacial bones, membranes, and fluids and extending to the sacrum and the rest of the body. Sutherland stated five principles:

- Inherent motility of the brain and spinal cord
- Rhythmic fluctuation of the cerebrospinal fluid
- Motion of dural membranes
- Articular mobility of the cranial bones
- Articular mobility of the sacrum between the pelvic ilia.

Practitioners palpate subtle movements of the cranial vault and other structures to assess the cranial rhythmic impulse and to prompt its balancing. From the standpoint of osteopathic philosophy, return of wholeness to the person is the ultimate goal of this therapy. The physiologic effects of this therapy have yet to be clearly elucidated in the medical literature.

Individuals using craniosacral therapy typically seek relief from pain and functional problems such as balance deficits. There is very limited medical literature on craniosacral therapy and only one study of craniosacral therapy for brain injury. Most of the studies look at inter-rater reliability and reproducibility as well as documenting an abnormal cranial rhythm (110). Greenman et al. (1995) studied the cranial rhythmic impulse in 55 patients with traumatic brain injury as part of their assessment and treatment within an outpatient rehabilitation program. The author notes that cranial osteopathy has been empirically shown to be effective in the treatment of patients with traumatic brain injury. The study documents the cranial impulse slower than average with typically encountered cranial strain patterns noted in 97% of the patients. Three of the patients (5%) seized during treatment. Other unlikely adverse reactions reported include mild headache, exacerbation of vertigo, and visceral symptoms. Due to this seizure risk and adverse reactions, consideration of the practitioner and setting where craniosacral manipulation is performed should include preparedness for these events. Both the positive outcomes and adverse side effects suggest that cranial osteopathy affects the autonomic nervous system. Patients who have participated in

this treatment commonly report profound relaxation suggesting a parasympathetic activation. This was evaluated by Robbins (1996) (111) in a randomized controlled study of 6 normal individuals. Each subject underwent four interventions. The active treatments were cranial osteopathy on the head and cranial osteopathy on the sacrum. The control treatments were no touch and light touch to a different area of the body. The order of treatment and controls was randomized and each subject underwent the whole protocol twice with washout periods between interventions. Cranial therapy at the head, as opposed to treatment at the sacrum, produced significantly higher parasympathetic activity than no touch or light touch. In conclusion, despite patient reports of osteopathic cranial therapy and its variations having effectiveness in post traumatic headache, anxiety, and balance deficits, the paucity and quality of research on craniosacral therapy as reviewed by (112) Green (1999) do not support its effectiveness.

## SPIRITUAL HEALING

Many individuals respond to illness and impairment by turning to prayer and requests for spiritual healing. Rehabilitation by its very nature seeks to motivate the patient and family members to produce the best possible functional outcome. Traumatic brain injury often occurs at a young age leaving people and their social support network with many years of living within a void replacing their previously functional lives. Maintaining hope in spite of this challenges the best of people. Prayer has been a traditional means of keeping a positive, constructive outlook in the face of despair. Prayer has an extensive literature that was reviewed in Larry Dossey's book *Healing Words* (113). In this book the author demonstrates the positive effect of prayerful intention on health across a number of clinical conditions. He notes that prayer is both non-local and not bound by time. Effective prayer may cross great distances or incredible boundaries. The time of prayer may be unrelated to the time of its need by the individual receiving prayer.

Harold Koenig wrote about spirituality and religion as a practical part of patient care (114). In this excellent book he addresses issues that arise when considering discussing patients' spirituality including boundaries, means to begin the discussion, and possible outcomes based on a review of medical literature. Three simple questionnaires discussed and in use today are the FICA spiritual assessment tool (115), the HOPE questionnaire (116), and the ACP Spiritual History (117). These tools can be used as part of the psychosocial history during patient interviews. Collecting this information serves as a means to let the patient know that their beliefs are valued and may strengthen the therapeutic relationship between the



clinician and the patient. If the patient desires, the information is used to refer the patient to the hospital chaplain, a pastoral counselor, a clergy, or another person within their spiritual or religious community. Patients use religion and beliefs to cope with illness. In a review of more than 1200 articles from the 20th century evaluating the association between religion and health, Harold Koenig found that the vast majority of them showed a positive association (118). Medical literature suggests that patients do want to discuss how their spirituality and beliefs play a role in the recovery from illness and relief from impairment (119).

The shaman or community medicine man probably represents the oldest spiritual healing tradition dating back to pre-historic times. Historically the shaman represents a cross-cultural approach to the diagnosis and treatment of illness. This has traditionally been a culturally bound practice. Western contemporary shamanic practitioners may practice without a culturally bound approach. From the practitioner's perspective, the patient with traumatic brain injury who reports an abrupt personality change, a sense of loss or void, and depression suggests a profoundly spiritual component of illness. The practitioner may suggest that the patient had partial soul loss. During the traumatic event, the part of the person's soul fled as a survival mechanism. This would be described as dissociation in psychological terms. Another complaint of depression, loss of personal drive, lack of interest in life, and overall misfortune may be the result of spiritual power loss. The practitioner would approach these spiritual illnesses by attempting to retrieve them and reinstating them to the patient. Individuals with BI who have attempted these spiritual healing approaches have reported return of previous personality, relief of depression, increased sense of life's worth and improved energy level. Herbert Benson (120) proposes that spiritual healing could be a magnification of the placebo effect whereby, because the individual thinks that something will work, it is effective. This may be an appropriate mechanism for those interventions when a person knows something was done to them or for them. It doesn't explain non-local anonymous healing through prayer. Specific spiritual healing techniques besides prayer have little or no voice in the medical literature at present. Spiritual healing addresses the transpersonal element of returning to wellness. Individuals with brain injury commonly express a void in their life. This profound disconnection with the world is addressed through spiritual healing by re-connection to a whole greater than themselves. This affects individuals on a level responding to the questions of what happened to me; why did this happen to me; and does my life have any meaning anymore? By supporting the patient's spiritual and religious beliefs the physician expresses caring and compassion for the patient. In doing so the physician strengthens their relationship to the

patient, opens the door to more effectively motivate the patient and their support system, and allows for healing outside of the medical model.

## ELECTRICAL AND MAGNETIC THERAPIES

The relevance of magnetism to health care is only recently being explored in a scientific manner as demonstrated by the expansion of magnetic resonance imaging technology over the last twenty years. The history of magnetic and electrical therapy dates back into early recorded medical history. Dr. Frank Krusen, in his classic *Physical Medicine and Rehabilitation* (121) notes the medical reference to electrical therapy dated to about 2000 years ago:

Electrotherapy was inaugurated in the reign of the Roman Emperor, Tiberius (14 to 37 CE). Anthero, a freedman, during a walk at the seashore, stepped on a torpedo (an electrified fish) and was thus "freed of gout."

About 50 CE, the physician Scribonius Largus recommended repeated applications of the electric-ray fish for the treatment of headache and neuralgia. In 78 CE, Pedanius Dioscorides recommended shocks from the torpedo fish for intractable headache, a procedure echoed by Galen in 200 CE. Moving away from the fish itself, Aetius in 450 CE recommended that a patient with gout hold a magnet as a treatment. Paracelsus (before 1541 CE) observed that the magnet has "power over the matter of all diseases." It was William Gilbert however who became the father of magnetic therapy, Gilbert published "De Magnete" (Of the Magnet) in 1600 CE and was appointed "chief physician in personal attendance on Queen Elizabeth" the next year. Gilbert also coined the term "electric", derived from the Greek name for amber. Magnets have been used in shoes and wristbands purportedly to help pain. Electromagnetic fields are commonly used to facilitate bone healing in the setting of a non-union, particularly of the tibia or spine. There is also limited research behind advocating magnets for various other medical conditions including wound healing, pain in the limbs, and muscle recovery after exercise (122). Unfortunately numerous claims in the lay literature that magnetism promotes healing are not supported in the available scientific literature to date.

Transcranial magnetic stimulation (TMS) is a widely available, painless and safe technique with a good sensitivity for both corticospinal and corticobulbar tract abnormalities. Owing to the low sensitivity of clinical signs in assessing upper motor neuron (UMN) disorders, there is a need for investigative tools capable of detecting abnormal function of the pyramidal tract. In TMS, an electromagnetic coil is placed on the scalp, high intensity

electrical current is rapidly turned on and off in the coil, through the discharge of capacitors, with the stimulation produced by this discharge of electromagnetic capacitors then causing either an increase or a decrease in the excitability of the affected brain structures. TMS may contribute to the diagnosis of motor neuron disorders by reflecting a UMN dysfunction that is not clinically detectable (123–128).

Electrical stimulation was and is still used on the brain by psychiatrists (Electroconvulsive Therapy, ECT) to treat intractable depression. It has been speculated that the pathophysiology of depression may include synaptic hypoactivity of the left prefrontal cortex (129). Recently, transcranial magnetic stimulation (TMS) has been used to treat depression. TMS has been shown to be effective in double-blind, placebo-controlled trial (130, 131) and it was as effective as ECT in another controlled trial (132).

In 2001, a meta-analysis was performed on 12 published and unpublished sham-controlled studies of left or right prefrontal cortical repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression (133). The study compared the decrease in Hamilton Depression Rating Scale (HDRS) achieved with rTMS and sham stimulation. The authors reported that rTMS was statistically superior to sham stimulation in the treatment of depression, showing a moderate to large effect size. However, the clinical significance of these results was modest and the differences in response to rTMS across studies was not clearly explained (134). A study by Triggs and others at the Human Motor Physiology Laboratory of the University of Florida Health Science Center at Gainesville looked for possible cognitive side effects associated with left prefrontal magnetic stimulation. They measured the effects of left prefrontal rapid TMS on mood, cognition, and motor evoked potential threshold in 10 patients with medication-resistant major depression. In a 2-week open trial of left prefrontal rapid TMS off antidepressant medications, scores on the Hamilton Rating Scale for Depression and the Beck Depression Inventory decreased by 41% and 40%, respectively. After resuming pre-TMS antidepressant medication, improvement in mood was still significant at 1 and 3 months later. In their study, TMS had no adverse effects on neuropsychological performance. Interestingly, TMS treatments were associated with significant decreases in motor evoked potential threshold in the 9 of 10 patients who remained off psychotropic medications during the 2-week treatment period (135).

In addition to its reported effect on mood, TMS has been studied in various types of motor pathology. From Italy, Cantello reported a use of TMS in movement disorders. Diseases for which TMS has been studied include Parkinson's disease, corticobasal degeneration, multiple system atrophy, progressive supranuclear palsy, essential tremor, dystonia, Huntington's chorea, myoclonus, the

ataxias, Tourette's syndrome, restless legs syndrome, Wilson's disease, Rett syndrome, and stiff-person (stiff man) syndrome (136). In a controlled study from Spain, Gironell reported that TMS over the cerebellum is helpful in the treatment of essential tremor (137). From his Neuro Communication Research laboratory in Danbury, Connecticut, Sandyk has used TMS extensively in Parkinson's disease (138). Various aspects of Parkinson's disease were studied with TMS in a series of experiments conducted by Sandyk. All of Sandyk's studies were reported in the journal he established, the *International Journal of Neuroscience*. Sandyk reported improvements with weak electromagnetic fields using TMS in PD patients with speech impairments (139–144). Some would argue that his studies are quite controversial because of their publication in non-refereed journals, the weakness of the employed magnetic fields (in picotesla), generalization from case studies of just one subject or a limited number of subjects, and the lack of any attempt at blinding the patient and observer.

Heldmann reported in 2000 that repetitive Peripheral Magnetic Stimulation (RPMS) is useful in the treatment of sensory/right parietal lobe deficits by helping to overcome tactile extinction (145). Reporting from the Technical University of Munich, Germany, they studied 14 patients with lesions in the right-hemisphere and tactile extinction. Patients were randomly allocated to an experimental or a control group. The experimental group received one single RPMS treatment of the left forearm as well as a condition of attentional cueing known to improve visual extinction. The control group, with comparable tactile extinction scores, neither received RPMS nor verbal cueing. In the experimental group RPMS led to a significant reduction of left-sided extinctions in the recognition of different tactual surfaces, but had no effect on ipsilateral errors. They felt that these results showed that sensory inflow is an important modulatory factor in tactile extinction. Moser and others at the University of Iowa found improvements in cognition—reporting that rTMS improved executive functioning (146). In their study, the cognitive effects of active and sham repetitive transcranial magnetic stimulation (rTMS) were examined in 19 middle-aged and elderly patients with refractory depression. Patients received either active ( $n = 9$ ) or sham ( $n = 10$ ) rTMS targeted at the anterior portion of the left middle frontal gyrus. Patients in the active rTMS group improved significantly on a test of cognitive flexibility and conceptual tracking (Trail Making Test-B). Roth et al. studied rTMS on knowledge acquisition in 20 normal subjects and found no significant difference in a group of normal subjects treated with 25 minutes of high-frequency left dorsolateral prefrontal rTMS compared to a sham untreated group for any memory acquisition. In the area of motor functioning, Fraser et al. at the University Department of Gastroenterology in Salford, United Kingdom, reported

that TMS can improve motor recovery following brain injury and speculated that the mechanism is improved plasticity of the motor cortex (147). They studied a group of acutely dysphagic stroke patients. TMS was used with varying patterns of input. They found that a specific pattern of magnetic stimulation induced the strongest cortical activation (and thus enhanced brain excitability) as measured by functional Magnetic Resonance Imaging (fMRI). This pattern was 5 Hz at 75% of the maximal tolerated intensity for 10 minutes. When this specific pattern of frequency, intensity, and duration of the magnetic stimulus was applied, a greater improvement in swallowing function was seen. This enhanced corticobulbar excitability was increased mainly in the undamaged hemisphere and correlated with recovery.

Others have likewise speculated upon and studied the mechanism of TMS. Conforto reported that TMS speeds central motor conduction time (148). As noted above, one study found that TMS treatments were associated with significant decreases in motor evoked potential threshold (149). Fraser and others wrote that TMS enhances plasticity of the motor cortex (150).

From the Max Planck Institute of Psychiatry in Munich, Keck and others reported that rTMS increases the release of dopamine in the mesolimbic and mesostriatal systems. These authors speculated that this increase in dopaminergic neurotransmission may contribute to the beneficial effects of rTMS in the treatment of affective disorders and Parkinson's disease. From the Montreal Neurological Institute at McGill University, Strafella and others reported that rTMS of the dorsolateral prefrontal cortex, but not the left occipital cortex, in healthy human subjects induces dopamine release in the ipsilateral caudate nucleus (151). They used [(11)C]raclopride and positron emission tomography to measure changes in extracellular dopamine concentration in vivo after repetitive transcranial magnetic stimulation (rTMS). In this study, there were no dopaminergic changes in the putamen, nucleus accumbens, or right caudate.

There is great controversy over the necessary intensity of the magnetic field for clinical effects to be seen. Sandyk uses electromagnetic fields that are so weak that some have questioned their efficacy. For cognitive deficits, he described using two successive transcranial applications, each of 20 minutes duration, with AC pulsed electromagnetic fields of 7.5 picoTesla flux density and frequencies of 5Hz and 7Hz respectively (152). For perceptual deficits, he describes using "AC pulsed electromagnetic fields (EMFs) in the picotesla flux density applied transcranially" (153, 154). For word-fluency deficits, he describes five patients in which he used "electromagnetic fields (EMF) of extremely low intensity (in the picotesla range) and frequency (5–8Hz)" (155). Also using a relatively weak magnetic field, Baker-Price and others studied four subjects with a history of persistent or frequently intermittent

refractory depression following a closed head injury. They applied a "weak" field that was actually 100 times the strength of that used by Sandyk:  $10^{-6}$  vs  $10^{-8}$  to the head of each (156). A one microTesla complex, burst-firing magnetic field was applied to the temporoparietal regions of the head for five 30-minute sessions over five weeks. Their results showed that significant improvement of Beck depression scores, while other emotional and physical parameters did not change. They note that their results "support converging theoretical and empirical evidence that very weak, applied complex magnetic fields whose wave structure and pulse patterns are congruent with groups of neurons within specific regions of brain volume can improve neurocognitive function in human beings." (157) On the other hand, most authors recommend magnetic fields of higher intensity. In most cases, the magnetic field is quite powerful and is in the range of 1–2 Teslas or 10,000 to 20,000 Gauss. This was originally used for brain mapping to test the domains of brain function in the range of 2–3 cycles per second (Hz). More recent machines have used increased frequencies at ranges up to 50 Hz (158). Fraser's study improving dysphagia used 75% maximal tolerated intensity at 5 Hz for 10 min (159).

Since the general technology for magnetic stimulation may not be patented, several companies exist that fabricate the devices. Each has their own patents on their particular coils. Two of the largest include; *Neuronetics*, *magstim.com*, *www.neuronetics.com*, *www.magtim.com* Richards and others noted "there are EM effects on biology that are potentially both harmful and beneficial." (160) Certainly this is true, yet there have been few reported complications with TMS. A literature review revealed one study which reported one case of a "pseudoabsence seizure" (161). As mentioned above, one study specifically looking for complications found TMS had no adverse effects on neuropsychological performance (162). Regarding strength of the electromagnetic field, the FDA had ruled that a limit of 80% of the level, which would cause neuron depolarization, was the maximum levels considered safe for application. It has been suggested that the frequency and variation of the field is more important than its strength. This is an issue that needs to be addressed with further research.

TMS is a new frontier in brain injury and the efficacy remains controversial even in psychiatry (163) and Parkinson's disease—where it has most frequently been studied. Yet reports of its possible effectiveness with low morbidity are encouraging. Patients with brain injury certainly have many of the problems for which TMS has been purported to work: depression, movement disorders, tremor, and parietal lobe syndrome. Nevertheless the high power magnets are expensive and the procedure is a not yet a covered Medicare service, also the technology is not yet widely available. It remains to be seen whether what

appears to be promising technology will be proven to be useful in brain injury.

Functional electrical stimulation (FES), sometimes referred to as functional neuromuscular stimulation (FNS) or neuromuscular stimulation (NMS), has both therapeutic and functional purposes, but excludes use in sensory systems. FES is used to stimulate nerves which innervate specific muscle groups to produce an effect similar to muscles in voluntary exercise. The clinical applications of FES in rehabilitation include muscle strengthening, improved range of motion, facilitation and re-education of voluntary motor function in orthotic training, and, inhibition of spasticity. It is believed that there are no absolute contraindications for FES though relative contraindications include individuals with cardiac arrhythmias, pregnancy, wounds that are healing (as stimulating muscle directly under healing tissues may be contraindicated), electrode sensitivity, or congestive heart failure. Occasionally these devices are implanted in the body to provide long-lasting effects, usually with electrodes at, or near, the spinal cord itself. FES is known to benefit paralysis of spasticity (UMN disorders) and is known to improve de-conditioned cardiovascular patients, and can function to facilitate improved limb movement. Neurogenic bowel and bladder have been shown to benefit from FES, as has sexual dysfunction, resulting from spinal cord injury, stroke, MS or closed head injury.

Transcutaneous electrical nerve stimulation (TENS) is a therapy that utilizes electrical current, usually direct current, delivered through electrodes which have been placed on the skin. TENS is used for pain relief, electrical stimulation of the nerves has been shown to encourage the body to produce endorphins, which function to block the perception of pain, both centrally and peripherally. TENS is performed with a battery powered device, attached to two or four electrodes by small gauge insulated wires, that then conduct the electrical current from the TENS unit to the area of pain. The placement is frequently in a rectangle, surrounding the painful area and the current generated by the device creates a circuit of electrical impulses that, travel along the nerve fibers, reducing pain. The machine can be set for various wavelengths, and frequencies. The individual's physical therapist or physician usually determines the settings. Used most often to treat muscle, joint and bone problems occurring with neuromuscular or musculoskeletal problems, TENS is often utilized for acute or chronic pain including low back pain, neck pain, tendonitis, or bursitis. Though considered generally safe, the machine could cause harm if misused, so TENS use is currently restricted to application only after physician prescription.

Cranial electrical stimulation (CES) is an experimental and an investigational therapy used for the treatment of neuropsychological disorders. CES uses microcurrent, pulsed high frequency carrier waves (15,000 Hz) in

a modulating action at low current levels to re-establish optimal neurotransmitter levels and functioning within the injured brain. The foundation of CES therapy is conversion of amino acids to neurotransmitters, improving the quality of neurotransmission (164). Its particular mode of functioning is as a corrective measure for brain dysrhythmia. After placement of electrode clips on each earlobe, the microcurrent pulses are thought to reach the brain via a perineuronal or vascular pathway, coursing via the auditory meatus to the thalamus, the primary center of activity. This cell membrane interaction occurs in a manner which then produces modifications in information transduction (physical energy conversion into nervous signal energy), as is associated with classical second messenger pathways, calcium channels and cyclic AMP (cAMP). Depression and anxiety have been shown to improve with CES use, as have hypertension and headaches. CES works in potentiating the effects of centrally-mediated analgesic drugs like fentanyl, morphine, and dextromoramide, thus aiding in chronic and cancer pain therapy. Neuroepileptic medication use in individuals with BI is decreased with CES therapies and the effects of general brain dysfunction and mood change subsequent to closed head injury appear responsive to CES (165). CES treatments are applied in the early hours, after awakening from sleep, avoiding use within three hours of scheduled sleep, to avoid a stimulative effect. Generally, CES is well tolerated, with no negative effects or major contraindications found for the use of CES, either in the US or in Europe. Rare paradoxical events occur, such as hyperexcitement, though this is unusual.

Electro-crystal therapy is a form of electrical therapy which involves the pulsing of electrical signals, through mineral crystals, in order to greatly amplify the crystals' inherent power. Crystal therapy works with the energy of specific crystals to clear blockages, both in the physical and auric bodies. This therapy uses resonance (one vibrating substance affecting the vibration in another vibrating substance) to re-establish balance in the ill or injured body, thus allowing the body the optimum opportunity of self-healing. Reportedly, after a crystal therapy session by a qualified crystal therapist, a great sense of relaxation and well-being is produced. A session alleviates tension and stress, bringing relief on the mental, emotional and physical plane. A tube of special crystals is placed over the area to be treated; then, the healing qualities of the specific crystals are magnified thousands of times by electrical signals passing through them. Electro-crystal therapy is believed to be beneficial in the treatment of stress and anxiety, headaches, musculoskeletal pain, spine pain, and chronic fatigue syndrome. There are no reported contraindications for the use of electro-crystal therapy and no reported adverse side effects are known.

Electro-homeopathy works according to the belief that there are two vital fluids present in the human body,

the lymph system and the blood system. Practitioners believe that any blockages in either of those two systems causes disease and illness. It is believed then that electro-homeopathic medicines can regulate this lymph and blood problem, thereby assisting healing.

### ALTERNATIVE MOVEMENT THERAPIES

The Alexander technique and Feldenkrais method are two popular contemporary alternative movement therapies used by individuals with BI. Both techniques are active treatment programs usually learned from a certified practitioner and performed by the patient. Both focus on awareness of movement and the person's inner emotional state associated with it. Frederic Matthias Alexander was a 19<sup>th</sup> century actor who lost his voice and developed his technique in response to observing how his uncoordinated movements and posture led to his voice loss. Alexander therapy consists of evaluating how common functional activities such as sitting, standing, and walking have muscular tension associated with them and then learning how to avoid triggering the muscular tension with the old pattern of movement. Attention initially focuses the individual's inner sense of movement and then progresses to shifting that sense to discover the release of tension with awareness of proper posture. By inhibiting those postural elements leading to tension the participant is able to recover greater fluidity of movement. No references were identified in a review of the medical literature specific to the application of Alexander technique to brain injury survivors. A randomized controlled clinical trial compared the Alexander technique, massage and no intervention on disability, depression, and attitude toward self, for patients with Parkinson's disease (166). The study showed statistically significant improvement in all three categories only in those patients treated with the Alexander technique.

Moshe Feldenkrais, a physicist, initially developed the Feldenkrais method based on his personal experience with severe knee injury. The therapy has evolved to a series of mat exercises and some touch-guided movement that together raise the awareness of the patient to their own movement patterns. Unlike traditional physical therapy techniques that desire a specific movement pattern as the outcome and train the patient toward the desired pattern, Feldenkrais's method seeks to support change through the deepest inner sense of the client's actual movement. A review of the medical literature did not provide any references specific to the application of the Feldenkrais method to brain injury survivors. The Feldenkrais method was compared to sham intervention for patients with multiple sclerosis using a crossover study design (167). Hand dexterity, anxiety, depression, self-efficacy, multiple sclerosis symptoms, performance, and

perceived stress were measured. The Feldenkrais method significantly decreased perceived stress and anxiety, but did not improve self reported function or dexterity. Both the Alexander technique and the Feldenkrais method use awareness based learning rather than repetitive physical exercise. They seek to produce more fluid movement and more choices in movement with greater conscious awareness of the potential outcomes for chosen movement patterns. Traumatic brain injury patients using these therapies report a greater sense of comfort during activity, more solidity in their standing and walking, and fewer complaints related to their neurologic compromise such as vestibular hyper-reactivity and paresis. Based on the types of interventions and exercises applied, the mechanism could be postulated to result from greater body awareness of posture and movement. Through this awareness the individual may inhibit muscular tension, poor posture, and gait disturbances. A review of the medical literature provides no documented effectiveness in brain injury, but a limited literature shows some success in application to other neurologic conditions

### HYPERBARIC OXYGEN THERAPY

Hyperbaric oxygen therapy (HBOT) is an established medical therapy for certain conditions and is increasingly being advocated for the treatment of neurological disorders such as cerebral palsy, multiple sclerosis, stroke, and traumatic brain injury (168). HBOT delivers 100% oxygen under pressure, which increases the amount of oxygen dissolved in the blood, thereby increasing the oxygen delivered to the body's tissues. HBOT may also enhance the formation of new blood vessels, decrease inflammation, and increase the volume of blood flow (168, 169).

Treatment sessions occur inside a sealed, pressurized space known as a hyperbaric chamber. The oxygen is delivered either by mask or directly into the chamber. The pressures used are expressed in units of atmospheric pressure and commonly range from 1.5 to 3 atmospheres. The sessions, often referred to as "dives", usually last from 30 to 90 minutes. Many practitioners recommend an average of 100 sessions (range 80–150) for the treatment of chronic, severe BI (168). Because the cost ranges from approximately \$200- \$400 a session, the total estimated cost of a full course of treatment is approximately twenty five thousand dollars. This amount is never covered by Medicare and rarely by commercial insurance. More the treatment of TBI is not recognized as an conceptual indication for HBOT.

Adverse events can be significant and are related to either the increased pressure or the high concentration of oxygen and include the possibility of seizures, pulmonary injury, and otic trauma. The incidence of seizures is thought to be about 1–2% in the non-neurological

population and is related to the duration of treatment as well as the pressures utilized (170). Pulmonary injury includes aspiration, infiltrates, or direct barotrauma and has a reported incidence of 10% to 30% (170). Otic complications such as pain or rupture of the tympanic membrane have an incidence of 5% to 10% (170) but may be prevented by temporary myringotomies. Additionally there is concern that a prolonged course of HBOT may result in subtle, long-term neurological deficits, although this has not been established (170).

Although the FDA regulates the hyperbaric chambers themselves as medical devices, there are no mandated national or local standards for the staffing or training of personnel. Even less regulation governs free-standing facilities because they are not covered under the regulations for hospitals. These issues are partially being addressed by a recent program of voluntary accreditation administered through the Undersea and Hyperbaric Medical Society. Treatment with HBOT requires a prescription from a physician. However, prescribing HBOT for the treatment of BI would be considered an "off-label" use, since BI, stroke, multiple sclerosis, and cerebral palsy are not FDA approved indications for HBOT. In fact, there are only thirteen FDA approved indications for HBOT among them carbon monoxide poisoning, air embolism, selected wounds, and decompression sickness.

Although many of these conditions are seen treated as HBOT for over 50 years, the use of HBOT has recently become even more common. There are over 500 HBOT centers currently operating in the United States. In addition, there is a major professional organization devoted to HBOT is the Undersea and Hyperbaric Medicine Society, which also publishes "Undersea and Hyperbaric Medicine". This organization, founded in 1967, now has over 2500 members. Board certification is offered by passing a subspecialty examination offered by the American Board of Preventive Medicine. Finally, there are two main textbooks in the field (168, 169). However, these organizations and publications focus almost exclusively on the accepted indications for HBOT and infrequently address the use of HBOT in the treatment of neurological conditions such as brain injury (BI).

The evidence for the efficacy of HBOT in the treatment of TBI, strokes, and cerebral palsy was extensively reviewed recently by the Agency for Healthcare Research and Quality (AHRQ) (170). The most authors of this report also published a separate review specifically addressing the evidence in TBI (171). The conclusions of these reviews were endorsed by the Undersea and Hyperbaric Medicine Society which also conducted their own review of the role of HBOT in the treatment of multiple sclerosis (172). In addition, a review of HBOT as a treatment for BI and stroke was also separately completed by an agency of the government of British Columbia (180). Finally, the Cochrane Database of Systematic Reviews

recently published their own reviews of the HBOT in TBI (174). All together, these reviews evaluated over one hundred papers that met their inclusion criteria.

In general, all of these reviews found that there was little evidence for the efficacy of HBOT for the conditions reviewed. In addition to TBI, the AHRQ report reviewed the role of HBOT in both stroke and cerebral palsy. For both these conditions, there were observational and uncontrolled studies that reported a significant benefit from HBOT. However, there were very few controlled trials (four in stroke and one in cerebral palsy) and none of them were rated better than "fair" by the AHRQ (on a scale of poor, fair, and good). Moreover, none of these trials demonstrated any benefit of HBOT treatment. Despite this, given the methodological limitations of the trials, the report concluded only that there was currently insufficient evidence of efficacy in these conditions (as opposed to evidence of lack of efficacy). The report by the agency of the provincial government of British Columbia reached a similar conclusion. The situation in multiple sclerosis is different to the extent that there have been many more controlled trials in this population (ten) and, with one exception, none demonstrated a benefit for HBOT treatment. Given the weight of the evidence, the review by the Undersea and Hyperbaric Society concluded that HBOT did not appear to be an effective treatment for multiple sclerosis (although they acknowledged that there may be subsets of patients who might benefit, especially with longer treatment periods).

In TBI, there has been only one controlled study in the past twenty five years (175). This trial was in the acute care setting and involved 168 severely brain injured patients randomized to receive either HBOT or standard treatment. The treatments, begun within 24 hours of injury, were 60 minutes in length and at 1.5 atmospheres. They were administered every 8 hours for two weeks or until the patient was either brain dead or could follow simple commands. On average, patients received 21 treatments. After one year, patients who received HBOT treatment had an almost 50% reduction in mortality (17% vs 31%). However, the proportion of those who were dead or severely disabled was unchanged (approximately 50% in each group). Thus, although mortality decreased, the rate of a favorable outcome was unchanged. This study was rated as "fair" by the AHRQ. The only other controlled trial, also in the acute care setting (176) was conducted in 1976. Unlike the later study, it did not find any statistically significant difference between the HBOT and control groups (although there was a trend towards better outcomes in the treatment group). This study was also rated as "fair" by the AHRQ task force. Unfortunately, it is difficult to apply the findings because the study was conducted when the care for TBI was substantially different than it is now.

There were also two uncontrolled acute care trials that reported on clinical endpoints (177, 178). Both

reported benefits to HBOT treatment; however, both had serious methodological flaws and were rated as “poor” quality by the task force. The remainder of the studies in acute TBI was all observational studies or case reports. Although promising, most of these studies used intermediate endpoints such as cerebral blood flow, cerebral metabolism, CSF biochemistry, and intracranial pressure (179–184) thereby limiting their clinical applicability.

In chronic TBI, there have been no HBOT trials in the past twenty years. In fact, there are only three case reports and two case series (excluding abstracts or conference proceedings) (185–189). One case series reported a benefit for HBOT but reported only on intermediate outcomes (e.g. measures of cerebral metabolism) (185). The other case series found in evidence of clinical benefit in chronic TBI (186). Of the case reports, one reported a benefit to HBOT treatment but involved a patient only 6 weeks post-injury, thus making it difficult to separate out the effects of natural recovery (187). Another case report involved a patient approximately six months after BI and reported a benefit to HBOT treatment. However, the patient was also receiving rehabilitative intervention, thus making it difficult to separate the contributions of HBOT treatment from that of rehabilitation and natural recovery (188). Finally, one case report noted no benefit of HBOT treatment, but the focus was only on measures of gait and postural stability (189).

The previously published reviews (170–171) agree that there is insufficient evidence to recommend the use of HBOT for the treatment of BI. The Undersea and Hyperbaric Medical Society released a position paper on the use of HBOT for chronic brain injury, traumatic and non-traumatic. This paper concluded that “the weight of the currently available scientific literature is not felt to support an endorsement of HBOT for chronic brain injury” (172). Likewise, the evidence based review by the government of British Columbia also concluded that “the scientific literature as reviewed up until August 2001 does not support the use of hyperbaric oxygen in the treatment of head injury or stroke” (173). This is in accord with the findings of the AHRQ. In the summary, there is little evidence currently to support the use of HBOT as a treatment for chronic BI, the evidence of benefit in acute BI is more formidably but too there clinical evidence. This situation marked accordingly patients about the use of HBOT more difficult. Indeed, BI clinicians may be facing a difficult dilemma as consumer demand for HBOT increases in the BI community. This increase in demand may be fueled by several different trends including the general population’s interest in alternative treatments, the continued lack of many effective treatments for chronic BI, and the aggressive marketing by many HBOT facilities. The fact that most families will have to pay for the treatments themselves (due to lack of coverage of HBOT for BI) further underscores the importance of advising patients and families appropriately. Recently,

guidelines have been developed to help clinicians better address the ethical dilemmas this situation raises (190). In addition to supporting the evidence-based guidelines reviewed here, the authors also emphasize the importance of continued research to establish definitively the role of HBOT in the treatment of BI. Until definitive research is conducted, the authors recommend a full discussion with patients and families regarding the current lack of evidence of benefit as well as the risks involved, including the substantial financial commitment involved.

The use of CAM techniques to treat common associated sequelae of brain injury remains controversial. There is a lack of evidence to date supporting the safety and effectiveness of many CAM interventions. Nevertheless we may anticipate that brain injury survivors and their families will continue to seek CAM interventions to treat the multitude of symptomatic sequelae of brain injury, particularly where conventional medical practices may fail to provide effective relief. While the majority of CAM interventions are relatively safe the risk associated with and potential adverse effects of drug interactions and certain CAM interventions such as HBOT and some electrical therapies can be significant. With the expanding research focus on CAM interventions we anticipate further elucidation of the benefits and risks of CAM interventions and the incorporation of evidence-based CAM into conventional medical practices. It is important for physicians to recognize that their patients may pursue CAM interventions and that knowledge of the potential benefits and risk is essential in order to provide patients with the information they need for effective and safe use of CAM practices within Western health care systems.

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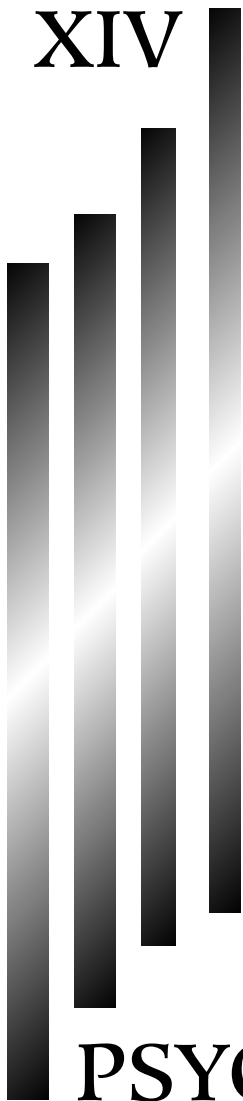


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XIV



**PSYCHOSOCIAL AND  
VOCATIONAL ISSUES**

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# 58

## Community Re-entry Issues and Long-Term Care

*Sally Kneipp  
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### **THE NEED FOR COMMUNITY RE-ENTRY SERVICES AND LONG-TERM CARE**

A little more than two decades ago, following the creation of the National Head Injury Foundation in Framingham, Massachusetts (now the Brain Injury Association of America), post-acute services for persons with traumatic brain injury (TBI) began to develop, slowly at first and then at an increasingly rapid rate. Family members of individuals with traumatic brain injury and interested professionals first met informally, and later through formal associations, to identify the needs and potential service delivery systems for persons in the post-acute phases of recovery, including those with long-term needs. As more individuals with traumatic brain injury were discharged to community settings, efforts were made to design programs that would meet their short- and long-term needs. The diverse post-acute needs of persons with traumatic brain injury and the differing abilities of families to provide the support needed by individuals with traumatic brain injury over the long-term, resulted in a burgeoning of post-acute programs.

The Commission on Accreditation of Rehabilitation Facilities (CARF) established standards for brain injury programs, with growing recognition of the post-acute service delivery options in community settings. Managed care initiatives by insurance companies resulted in significant reductions in the length of stay in hospitals and

facilities, resulting in much earlier discharges to post-acute programs (or to no additional treatment). Additionally, the 1979 Report of the United States General Accounting Office had emphasized the need for a redistribution in state and federal funds for persons with disabilities in institutionally-based programs (particularly, nursing homes) to services at home and in the community. In 1981, Medicaid Waiver Programs were initiated to reduce the cost of nursing home care and to foster more community-based services. By 1997, more than 500,000 persons with disabilities were reported to be receiving services through state Medicaid Waiver Programs. Twelve separate waiver programs had been established for persons with traumatic brain injury, and those states were serving 3,000 people in that category. Cusick, Gerhart, Mellick, et al. (1) reported that, among the Medicaid Waiver Programs, the expenditures were the smallest for the traumatic brain injury diagnostic group overall, but the amount spent on services per participant was greatest for that group because of the long-term sequelae of traumatic brain injury and the individuals' complex needs.

Venzie, Felicetti, and Cerra-Tyl (2) emphasized that, although legislative initiatives and managed care directives have been responsible in large part for the trend to more community-based programs, there has also been growing awareness of the clinical advantages of providing treatment in real-world settings. They discussed challenges

inherent in, and recommendations for, the establishment of community integrative brain injury programs.

Post-acute programs whose purpose was to facilitate the individual's return to the community were variously referred to as community-based, community re-entry, community integration, community reintegration, community integrative, and community-integrated programs. For example, in the CARF medical rehabilitation standards (3), there are several accreditation categories that may address community re-entry issues and long-term care, the focus of this chapter. They include the brain injury outpatient rehabilitation programs, brain injury home- and community-based programs, brain injury residential rehabilitation programs, brain injury long-term residential services, and brain injury vocational services. There are many providers who have not sought CARF accreditation but have well-established programs to address community re-entry and long-term needs. (Most of the administrators of those programs have stated that, while they acknowledge the importance and value of accreditation, their budgets are inadequate to cover the direct and indirect costs associated with the accreditation process.)

The differences in terminology used to describe these programs has led to some confusion about their scope and purpose, particularly on the part of individuals seeking services, family members investigating services, and payers who are exploring options for cost-effective services. Given the extensive treatment and care provided to persons with traumatic brain injury by emergency medical personnel, and multidisciplinary professionals in a variety of acute care, acute and other post-acute rehabilitation settings, many third-party payers have asked why such a broad spectrum of post-acute programs is necessary at the point of community re-entry if earlier treatment was effective, and why such services are necessary for such long periods of time (frequently, for many years or lifelong). *Enabling America: Assessing the Role of Rehabilitation Science and Engineering*, the 1997 report of the Institute of Medicine established by the United States Congress to evaluate existing rehabilitation models (4), pertains to all disabilities and is not intended to be specific to traumatic brain injury. Nonetheless, the conclusions and recommendations of the report have particular relevance to persons with traumatic brain injury at the point of community re-entry and address the need for services at this point.

The 1997 Institute of Medicine report refers to the disability model proposed by Saad Nagi in the 1950s and refined in the 1991 Institute of Medicine report, *Disability in America*. Dr. Nagi's conceptualization of the disabling process included four components: pathology, impairment, functional limitation, and disability. Further refinement of this model appeared in the 1997 Institute of Medicine report. This differentiated model of pathology, impairment, functional limitation, and disability was

revised to illustrate how biological, environmental (physical and social), and lifestyle/behavioral factors are involved in reversing the disabling process (i.e., rehabilitation, or the enabling process). The modified Institute of Medicine model presented the possibility of "no disabling condition," even in the presence of pathology, impairment, and functional limitation. The point made was that disability is not inherent in the individual; it can only be understood in relation to the interaction between an individual and his/her environment. It is precisely the challenge of achieving meaningful interaction with the environment that results in the need of individuals with traumatic brain injury for treatment to address community re-entry issues and long-term needs.

This point was underscored in 1998, when the National Institutes of Health (NIH) convened a consensus development conference on rehabilitation of persons with traumatic brain injury. The conference was followed by a press release and then a *NIH Consensus Statement* (5). As stated, the objective of the *NIH Consensus Statement* was to provide information on the findings of the conference to the biomedical research and clinical practice communities including, but not limited to, physicians representing many medical specialties, and psychologists. The Introduction of the *NIH Consensus Statement* emphasized that the greatest negative consequences following a traumatic brain injury are related to the individual's post-injury cognitive abilities and behavioral and emotional issues (rather than their physical impairments), since they compromise interpersonal relationships and impede participation in major life activities such as school and work.

Treatments mentioned for the cognitive, behavioral and emotional sequelae included cognitive rehabilitation therapy, assistive technology, psychotherapy, psychopharmacologic management, and manipulation of the environment to provide an optimal context for recovery and/or rehabilitation to occur. It was pointed out that treatments are provided in a wide range of settings, from rehabilitation hospitals to the home or community at large.

The significance of the consensus conference was that the conclusions were inclusive of the input of persons with traumatic brain injury, their family members, and nonmedical specialists in addition to medical specialists. The statement reflected the opinions of many persons associated with post-acute programs who had come to appreciate the importance, for positive outcomes to occur, of including many sources of input into the rehabilitation process. Some of the conclusions of the consensus conference relevant to this chapter were that:

1. the consequences of traumatic brain injury can be lifelong, even in cases of mild traumatic brain injury;
2. individually-tailored rehabilitation services should be modified to assure relevance as one's needs change over time;

3. extended care and rehabilitation for persons with traumatic brain injury should include community-based nonmedical services;
4. supportive services (e.g., respite care, counseling and in-home assistance) should be available to family members and significant others of individuals with traumatic brain injury;
5. modification of the individual's home, school, and work environments may be necessary to allow for increased participation in daily living;
6. the input of persons with traumatic brain injury, their family members, and significant others should be regarded as essential to the development and implementation of the rehabilitation program for each individual; and
7. consideration should be given to the timing of specific interventions, since the probability of a beneficial effect may be greater at some points in the rehabilitation process than at others. Moreover, recent investigation of the effects of aging following traumatic brain injury suggests the need for a service delivery system and specific treatments that can be provided when new clinical issues arise or become more pronounced as people age.

### Program Design and Treatment Models

While some post-acute programs continue to base their treatment on a multidisciplinary model, treatment based on an interdisciplinary model has been the norm over the past decade, with a growing number of post-acute programs designing treatment using a transdisciplinary approach. From a conceptual standpoint, treatment using an interdisciplinary or transdisciplinary model is particularly relevant and appropriate at the point of community re-entry, and long-term, since the most pressing need at this time is for the individual to be able to integrate the knowledge and skills acquired or re-acquired during earlier phases of his/her rehabilitation. Additionally, treatment must be designed with relevance to the unique characteristics of the environment in which the individual will live and function. Depending on the intermittent or chronic needs of the individual, treatment may be provided by a team of rehabilitation practitioners or by a single-service provider. The individualized nature of rehabilitation treatment is more evident at the community re-entry stage of the rehabilitation process than at any other time. The value of a holistic treatment approach in maximizing potential outcomes has also been recognized.

Malec and Basford (6) summarized the state of the art in post-acute brain injury rehabilitation programs in the mid-1990s. While acknowledging limitations of the study from a research design standpoint, the authors provided a categorization of types of post-acute programs and presented a model of brain injury rehabilitation. This

model, identified as an algorithm of level of rehabilitation care after traumatic brain injury, also appeared in a subsequent publication in 2003 (7). However, of concern is the component in the model designated "No services, or community-based services only." Particularly in the past decade, there has been growing awareness of the effectiveness of community-based services offered in the home and community (of the individual with traumatic brain injury), that are goal-oriented and ecologically valid treatment options. They are on a par with the other categories of the model (i.e., outpatient community re-entry, comprehensive/holistic day treatment, residential community reintegration and neurobehavioral) and should be clearly distinguished from "no services."

In describing the contributions of postacute neurorehabilitation to a national information system, Evans (8) explained that postacute providers frequently regarded the environment of the individual with TBI (i.e., the individual's home and where he/she spends time, such as in school, at the workplace, in the community at large) to be an extension of the treatment setting. Understanding the characteristics and dynamics of the individual's "world" was considered to be essential to the development of treatment approaches of optimal value. In these naturalistic settings, the concept of the treatment team was enlarged to include persons such as the individual's family members, teachers, employer, neighbors, etc. A shared information system is advocated as a means of facilitating the delivery of beneficial services and cost-effective outcomes.

In their article on the development of systems of care for persons with TBI over the past 20 years, Cope, Mayer and Cervelli (9) point out that the conceptualization of a comprehensive system of care now includes therapy and supported living in one's natural environment, perhaps throughout the individual's life. They identify cognitive and behavioral impairments as the focus of comprehensive therapy at this stage and acknowledge the benefits of treatment protocols delivered in the home and community of the individual with TBI to develop his or her ability to carry out activities of daily living and increase social opportunities. They recognize the use of a person-centered context to assist individuals to attain their life goals, and the value of community-based interventions such as "clubhouses" and peer support in improving long-term outcomes. They also recognize the role of psychopharmacologic and neuropharmacologic interventions.

Community re-entry and long-term needs must be addressed if an individual with traumatic brain injury is to achieve a satisfactory quality of life through purposeful, productive activity. Berube (10) explained that The Brain Injury Act, as amended in 2000, mandates exploration of interventions that will facilitate school and work re-entry and reintegration in the community. However, the process of meeting these needs is complicated by the



extremely heterogeneous nature of traumatic brain injury, the prominent role of cognitive and psychosocial deficits in eventual rehabilitation outcome, and the fact that a traumatic brain injury in any family member will impact on the family system and others who relate to that individual to any degree.

When determining the optimal treatment program to address the community re-entry and/or long-term needs of an individual following TBI, the most fundamental question is whether a residential or non-residential brain injury program is indicated. In making this decision, an analysis of the individual's home environment and family system must be made, to assure the likelihood that the environment will be able to reinforce the goals of the therapy program and that the level of any supervision needed will be sufficient to assure the individual's safety. Within the scope of residential programs, a wide range of options is available to address the individual's short- and long-term needs. The spectrum of options may range from intense, highly-structured clinical protocols with 1:1 staff/client ratios for individuals with significant behavioral problems to comprehensive transitional living programs to prepare individuals for independent living, or supported living programs offering considerable flexibility, much less structure and only periodic check-ins by staff. Persons with brain injury who also have pre- or post-injury histories of alcohol or drug abuse may require residential treatment in a program designed specially to address those needs, with services provided by staff with particular expertise in substance abuse. Within the comprehensive program, there is typically flexibility to move the individual from one clinical program to the other, as may be needed. Although the services may be designed along a continuum, from the most intensive to least intensive therapeutic support, the reality is that rehabilitation following brain injury is not always linear and various treatment protocols may need to be tried.

Non-residential programs at the community re-entry or long-term stage may also offer an array of options (from comprehensive day programs offering such services as occupational therapy, physical therapy, speech therapy, psychotherapy, cognitive rehabilitation therapy, vocational services, recreational therapy, etc.) to very individualized, goal-directed programs carried out in the individual's milieu (i.e., home and community). These therapy programs have a rehabilitation focus and are different in purpose from home health programs, although home health services may also be indicated for some individuals due to needs for physical assistance with self-care and activities of daily living and/or the need for supervision due to cognitive-communication, behavioral and/or emotional issues.

Because of the highly heterogeneous nature of traumatic brain injury, there must be an array of treatment options available to address community re-entry and

long-term needs. The state-federal vocational rehabilitation program, operated in accordance with a state plan, is a frequent resource for persons wishing to return to work. [Note: Employability and placeability are major concerns of persons with traumatic brain injury and their families; for more information on vocational issues, please refer to Chapter 61 in this book.] Incentives in relation to employment are available to persons receiving Social Security Disability Insurance (SSDI) and Supplemental Security Income (SSI) because of a disability or blindness. According to a home page of the Social Security Administration (SSA), *The Work Site* (11), the Ticket to Work and Work Incentives Improvement Act of 1999 led to the awarding of 119 cooperative agreements to community organizations to establish Benefits Planning, Assistance, and Outreach (BPAO) projects. The goal is to assist persons receiving SSDI or SSI to make informed decisions about working. Social Security Online also makes available, through its electronic booklet, "The Ticket to Work and Self-Sufficiency Program," answers to questions asked frequently by participants in this new SSA program (12).

The Brain Injury Association of America (BIAA) and its state affiliates offer an extensive array of services to persons with brain injuries, their family members, professionals and the community at large. Of particular value have been the support groups (normally held once a month at various locations), family support services and mentoring projects, and the *National Directory of Brain Injury Rehabilitation Services* (13).

### **Efficacy of Community-Based Programs**

While the growth of community-based programs has been substantial, demonstrating the efficacy of such programs has been exceedingly difficult. Minnes, Carlson, McColls, et al. (14) acknowledged that community integration is an often-used outcome measure in rehabilitation research and underscored that is understandable since the aim of rehabilitation is to remove barriers to individuals' participation in daily living. They studied the relationship between community integration and salient variables that included impairment, activity, participation, quality of life, paid support and informal support. Their findings revealed the complexity of community integration and the difficulty of measuring it. They emphasized the importance of clearly defining community integration in research projects and recommended the use of subjective as well as objective measures. They also discussed the methodological difficulty of using questionnaires with research participants who have cognitive impairments and recommended that survey items be read aloud to the participants and that, with permission, collateral informants (e.g., family members) be present to increase the probability of accurate responses.

Goranson, Graves, Allison, and La Freniere (15) emphasized that the demand for accountability by payers is resulting in closer examination of the cost-effectiveness of traumatic brain injury programs offering cognitive rehabilitation therapy. They point out that functional outcomes and life satisfaction should be improved as a result of therapy to improve cognitive abilities and coping skills, but that it is difficult to establish the efficacy of such programs because of problems developing a suitable research methodology, the non-comparability of the outcome measures (given the heterogeneity of the population and the individualized treatment plans), and lack of a multidimensional analysis.

Dawson, Levine, Schwartz, and Stuss (16) acknowledged the extreme variance in outcomes and emphasized the importance of predicting real-world outcomes when establishing clinical goals. They advocated for more specific predictors of recovery (such as attention and memory and other salient variables such as coping style) rather than injury severity, and the need to find out if better long-term outcomes would be achieved by addressing process-specific variables (e.g., pre-injury personality characteristics) during the acute phase.

The difficulty conducting research with experimental or even quasi-experimental research designs during the community re-entry phase of rehabilitation has led to a limited amount of data demonstrating the efficacy of community re-entry programs. As a result, some third-party payers have denied funding for needed services on the basis that there is insufficient empirical evidence of the cost-effectiveness of the treatment. This is particularly true in relation to cognitive rehabilitation therapy, which has been a standard component of most brain injury rehabilitation programs, including community re-entry programs, for over two decades. In denying funding for cognitive rehabilitation therapy, some payers have described it as “investigative,” “experimental” or “educational,” failing to realize that addressing neurocognitive deficits is crucial to maximizing functional recovery following brain injury.

### **Treatment in Real-life Contexts**

Cicerone, Dahlberg, Kalmar, et al. (17) pointed out that, even following moderate or good recovery neurologically, one’s quality of life following traumatic brain injury may be severely compromised because of persistent cognitive deficits and maladaptive behavior. The real-life context for any given individual following traumatic brain injury must be taken into account in order to achieve a satisfactory interface between the individual and his/her environment. Cicerone and Tupper (18) emphasized that the goal of rehabilitation after brain injury must be improvement in the ability to function in real life (not just in a therapy setting) and requires learning new ways to perform daily activities in a variety of contexts. However, the individual’s

cognitive deficits may impede the ability to benefit from traditional therapies, function successfully in daily living, and learn new ways to accomplish everyday tasks. There is a need for innovative therapeutic approaches in post-acute brain injury rehabilitation and for assurance that the approaches have true relevance to the individuals’ lives, particularly at the point of community re-entry.

Gordon and Hibbard (19) concluded that evaluation studies and anecdotes confirm the benefits of cognitive rehabilitation and cognitive remediation if individualized to meet the specific needs of the individual and delivered systematically and creatively in an appropriate context. They emphasized that the treatment can be demanding for the individuals and team members, and that the intensity and duration can be significant, but that it is evident that the treatment helps individuals to adapt to challenges of daily living after a traumatic brain injury.

### **Funding for Community Re-entry Services**

Funding for community re-entry services and long-term care comes from a variety of sources, which are frequently blended. Because the majority of traumatic brain injuries occur in motor vehicle accidents, the personal injury protection (PIP) portion of auto insurance policies is a major source of funding in many, if not most, states. Workers’ compensation insurance is another large source of funding, following work-related accidents (e.g., falls). Funding for some community re-entry services is available through private long-term disability plans and some health insurance carriers, but not all. Examples of other typical sources of funding include money set aside in structured settlements for rehabilitation purposes, private pay, programs operated with state and federal funding (e.g., the Division of Developmental Disabilities, Medicaid Waiver Programs, other waiver programs, crime victims’ boards, vocational rehabilitation agencies, recently-established traumatic brain injury funds), and voluntary agencies (brain injury associations).

Many insurance companies employ or contract with case managers (usually rehabilitation nurses) whose responsibility it is to assist the claims personnel in making decisions about the suitability of services recommended for the individual and the reasonableness of the costs for the services. They serve as external case managers to the programs offering the services; the programs may also employ internal case managers to assist program personnel in determining what services the individual will receive and assuring the availability of funding for reimbursement of costs for services rendered.

### **PREVALENT COMMUNITY RE-ENTRY ISSUES**

Among the many community re-entry issues for individuals following traumatic brain injury, family adjustment,

social isolation, limited community mobility, and barriers to employment are paramount. (Please see Chapter 61 for a discussion of vocational issues.) Even given the impetus of legislative initiatives such as the 1990 Americans with Disabilities Act, intended to facilitate the inclusion of persons with disabilities in society, the reality is that many individuals with traumatic brain injury remain homebound a large majority of the time, cared for by family members and significant others who are experiencing caregiver burden.

### Family Adjustment

The normal developmental stages and transitions in family life are disrupted following the brain injury of any member of a family. Significant changes in the usual roles and functions occur, and are often permanent. If not addressed adequately, these issues (discussed by Sander in Chapter 60 of this book) result in a diminished quality of life for all persons involved. As stated in the *NIH Consensus Statement* (20), there are serious social consequences following traumatic brain injury at any level of severity. There are risks of prolonged unemployment, financial hardship, divorce, criminal activity, substance abuse, and suicide. In addition to the strain on families, the resources of social service agencies and legal systems are strained. The negative effects of the traumatic brain injury may become more evident, and more severe, following the individual's unsuccessful attempts to resume his/her usual roles and responsibilities. Psychosocial issues become evident in family members and significant others as well as the individual with the brain injury; family dynamics are frequently unsatisfactory and family functioning deteriorates. In some situations, particularly if not addressed, these problems worsen over time.

Results of a survey conducted by staff of a community re-entry program, and presented at a national brain injury symposium, supported the assertion of Williams and Kay (21) that, even at the point of community re-entry, after considerable treatment has been provided, family members are usually not prepared to cope with the persistent cognitive, psychosocial, and/or emotional problems of their family member with traumatic brain injury. Rider-Williams and Trout (22) identified the following characteristics of the individual's traumatic brain injury to be the greatest challenges for family members: problems remembering; social isolation; problems planning and organizing; poor judgment; mood swings; difficulty paying attention and concentrating; poor problem-solving; fatigue; problems with balance and coordination; poor decision-making; not being able to walk like before; and impulsivity. Rider-Williams and Trout concluded that much needs to be done to help individuals with TBI and their family members cope with the numerous long-term challenges of TBI. They emphasized that, given managed

care initiatives and the decreased inpatient stays in rehabilitation hospitals and facilities, there is insufficient time for hospital personnel to provide as much patient/family education as was typically provided in the past, prior to discharge. Moreover, even when patient and family education was available, family members and significant others may not have been able to process the information yet. Treatment providers must be sensitive to family members' needs for timely information throughout the rehabilitation process.

Laroi (23) discussed the value of family therapy sessions even after active rehabilitation treatment, to help the family be aware of, and seek attention for, any negative changes in the family system. Family therapy in the home was recommended as a way to facilitate timely changes following disruptions in the family system. Strongly advised were selection of a family therapist with expertise in brain injury rehabilitation and close collaboration between the family therapist and the professionals providing the individual's brain injury rehabilitation therapy.

Kosciulek and Pichette (24) conducted a survey of primary caregivers of individuals with TBI in an attempt to isolate factors that enhance care. They found that supportive friends; a positive family outlook; availability of family support; and family unity, loyalty, and cooperation were variables that had a positive correlation with care. The unavailability of respite services, an absence of vocational rehabilitation services, limited assistance for meeting day-to-day needs, inappropriate living situations, and emotional and behavioral problems in the injured family member were identified as variables impacting negatively on care. Kosciulek and Pichette concluded that family members of persons who have sustained a TBI require an array of support services if they are to provide a high quality of care over an extended period. They also suggested that family satisfaction may improve quality of life and contribute to positive rehabilitation outcomes.

Godfrey, Harnett, Knight, et al. (25) examined the impact on caregivers when personality changes in the individual with TBI are due to problems with emotional control or problems with motivation, and contribute to caregivers' distress, burden and depression. The Head Injury Behaviour Scale was found to have good internal consistency and reliability and to be a reliable and valid measure of caregiver distress.

Ponsford, Olver, Ponsford, and Nelms (26) also discussed the emotional burden of caregiving, the effect on family adjustment, and the need to develop models of long-term support that will help reduce caregiver burden on family members and relatives. To learn what will be most effective, they recommended studies of the attributes, values and coping styles of families who adjust well following the traumatic brain injury of a family member.

### Social Isolation

Following a traumatic brain injury, many persons experience profound social isolation that severely compromises their quality of life. Burleigh, Farber and Gillard (27) pointed out that individuals with a TBI may have difficulty fulfilling or resuming an accepted social role, or simply may not be able to do so because of psychosocial deficits and/or emotional issues. They emphasized that rehabilitation treatment for these individuals should include the skills needed to develop and maintain interpersonal relationships, since otherwise they may become socially isolated and experience a low quality of life. They also pointed out that dissatisfaction with life could lead to psychological problems in addition to already-existing post-injury problems.

The goal of social integration should be part of the individual's treatment plan at the point of community reentry. A study by Brown, Gordon and Spielman (28), undertaken by a Research and Training Center on Community Integration of Individuals with Traumatic Brain Injury, focused on social and recreational activities of persons with traumatic brain injury (TBI) that required individuals leave their homes to engage in the activity and that addressed their social goals. Sample results of the study, based on self-report during interviews, revealed that the TBI sample (N = 279) was significantly less active than the no disability (ND) group (N = 244) on the composite measure of social-recreational activity and on each of the five indicators of social-recreational activity. The authors point out, however, that substantial within-group variance suggests the need to examine more closely what constitutes disadvantage in social participation. The authors also suggest that depression and fatigue, which frequently account for reduced social participation, should be addressed and that involvement in educational or work activity (either paid or volunteer) will provide additional opportunities for persons with traumatic brain injury to participate in social and recreational activities.

### Limited Community Mobility

Following a traumatic brain injury, access to the community may be limited dramatically. Sequelae of traumatic brain injury may compromise the individual's ability to get around safely in the community by driving a motor vehicle, riding a bicycle, using public transportation (i.e., bus, train, taxi cabs or trolley), using specialized transportation (e.g., paratransit services), or simply walking. Physical or sensory impairments restricting community mobility may include gait and motor incoordination, balance problems, visual deficits, audiovestibular dysfunction, communication deficits, bladder and bowel dysfunction and conditions such as post-traumatic epilepsy. Cognitive deficits impeding community mobility may include such problems as distractibility; limited

attention and concentration spans; poor memory; inadequate planning, organizing, decision-making and problem-solving skills; limited safety awareness and judgment; poor topographical orientation; impaired time awareness; and slow processing of information. Behavioral deficits such as apathy or lack of ability to initiate purposeful behavior, or behavioral excesses such as impulsivity or disinhibition, may also compromise one's community mobility. Limited stamina and endurance, and fatigue, are also moderating variables in one's ability to access the community.

*Driving after Traumatic Brain Injury* The sequelae of traumatic brain injury often make driving after a brain injury an unattainable, although highly desired, personal goal. The inability to drive a motor vehicle is a particularly distressing circumstance for late adolescents and young adults who comprise the greatest percentage of individuals with traumatic brain injury and who are frequently at important points in their career development. It is easy for anyone who drives to appreciate how an inability to drive can alter the ability to perform usual life roles. The inability to drive contributes to the major post-injury challenges of returning to work or school, resuming family roles, and reducing social isolation. The inability to drive can lead to lowered self-confidence and self-esteem and negative self-image, as it limits one's ability to function independently and access one's community. In rural areas, one's inability to drive is particularly problematic, since it usually results in a significant decrease in community involvement and/or significant demands on caregivers who must provide necessary transportation. Nonetheless, caregivers, as well as involved medical and non-medical professionals, must guard against making recommendations for driving based on sympathy for individuals whose attainment of personal goals is unquestionably complicated by the inability to drive. Decisions about one's driving privileges must take into account the public's right to a reasonable standard of safety. The public interest is protected, as well as the individual's, when there is a means for the individual to demonstrate the capacity to drive safely. Galski, et al. (29) summarize

What is known about the residual effects of brain injury on driving has been derived from studies attempting to show the ways and extent to which specific deficits relate to driving performance. A basic but ever-growing compendium of deficits has been compiled, including, but not limited to, *sensory deficiencies*, such as defects in visual and auditory acuity, glare and contrast sensitivity, and motion perception; *motoric difficulties*, such as loss of or reduction in strength, coordination, and reaction speed; *cognitive impairments*, such as poor visual scanning of traffic and environment, difficulties in spatial perception and

orientation, slowness in information processing, and loss of attentional abilities; and *personality or behavior disturbances*, such as accident-proneness, anxiety, or confusion in the face of complex driving situations or problems (p. 896).

Executive functions (discussed by Cicerone in Chapter 41, and Eslinger in Chapters 42 of this book) are especially salient variables in driving. Self-awareness is crucial to one's ability to predict whether he or she will be able to drive safely. In studying the predictors of outcome after traumatic brain injury, Coleman, Rapport, Ergh, et al. (30) found that the significant other or caregiver is more likely than the individual with traumatic brain injury to determine whether and how much driving will be done post-injury. They concluded that family education provided in a rehabilitation setting could facilitate family members' and significant others' understanding of the abilities needed to drive safely; because driving is such a common activity, the complex cognitive demands may not be recognized. Of value would be helping them to make observations of the individual's behavior and its implication for driving. For example, family members and significant others who report that the individual is having post-injury problems with frustration, anger or impulsivity, could be helped to anticipate the potential risks of driving if exhibiting those behaviors. While it is expected that the implications of those behavioral excesses for driving would be easily understood (particularly with attention in the media to "road rage"), other behaviors, such as lack of initiation, mental inflexibility, and perseveration may need much more explanation.

In many states, physicians are regarded as possessing the knowledge to make reasonable decisions and implement statutory restrictions regarding an individual's fitness to operate a motor vehicle post-injury, whether compromised by recurrent seizures, physical impairment or only by cognitive impairment. State licensing statutes and regulations regarding driving after cerebral injuries vary, but typically require demonstration of adequate visual acuity, perceptual ability as required to respond in a timely manner to traffic control devices, knowledge of traffic laws, and skills to operate a motor vehicle. Krauss, et al. (31) provides two useful tables—one summarizing the state regulations regarding driving and epilepsy (see Table 58-1) and the other summarizing driving regulations in states with flexible driving restrictions (see Table 58-2). Physicians are strongly recommended to be aware of the regulations which apply in their region, and to discuss thoroughly the matter of driving with their patients and guardians. Some physicians may not possess the knowledge of driving capabilities per se or the ability to test driving competency in a real-life situation, and may be prone to inaccuracy when extrapolating from an office examination to a real-time driving experience. In such cases, the

individual should be referred to a qualified driving evaluator with particular expertise in the assessment of driving capabilities following traumatic brain injury.

Such driving evaluations, consisting of driving simulations and then on-the-road ("behind-the-wheel") driving observation by a therapist or trainer sensitive to the issues of cerebral impairment, may be available through rehabilitation facilities. Following the driving evaluation, the physician analyzes recommendations in relation to his/her own medical knowledge of the individual, and thereby renders an opinion about fitness to drive.

Although requiring that a driver demonstrate adequate knowledge of pertinent laws and regulations, the standards of the state motor vehicle department may be relatively minimal in relation to physical abilities. For example, it may be minimally adequate to have visual acuity of 20/40, even if extemporaneous binocular or depth visual processing is impaired. It is likely that a state driving examiner will not anticipate the difficulties an individual with a brain injury may have in making rapid decisions, filtering complex simultaneous stimuli, or adapting in unpredictable situations. The physician, on the other hand, because of the understanding of brain function under the circumstances of challenge and duress, may need to take a more critical view of driving safety than does the state. The physician should be aware of possible adverse affects which treatment may have on driving, such as sedating side effects of medications, and make patients aware of these effects as potential restrictions to driving.

While physicians have a responsibility to protect third parties from potential harm, in some states issues of privacy and confidentiality may arise if the physician notifies legal authorities without the consent of the individual. Drazkowski (32) points out that the requirement to notify authorities may discourage patients from disclosing to their physicians the frequency and intensity of their seizures, and that could lead to inadequate medical care. Nonetheless, a physician's obligation to report patients who are engaging in illegal activity or pose the risk of danger or harm to the public at large takes precedence over issues of confidentiality.

With respect to seizures, Drazkowski recommends strongly that the physician take into account how anti-epileptic drugs [AED] might affect driving capacity, the risk of AED non-compliance or discontinuation, initial reporting requirements at the time of diagnosis, and the need for adequate medical information to be provided subsequently to regulatory agencies, if called upon.

Although developed with specific reference to another medical condition with motoric, perceptual, cognitive, and executive function impairment (namely, Huntington's disease), the driving assessment developed by Rubin (33) may be useful to a physician (or other professionals) in arriving at an opinion of one's ability to

**TABLE 58-1**  
*Driving and Epilepsy: Regulations and Practices of US States\**

STATE	LEGAL SEIZURE-FREE RESTRICTION (MO)	RARE EXCEPTIONS TO SEIZURE-FREE INTERVAL BASED ON MITIGATING FACTORS†	REQUIRED MVA MEDICAL REVIEW, TYPE OR INTERVAL‡	MANDATORY PHYSICIAN REPORTING	MVA LICENSE APPEAL	PHYSICIAN LIABLE FOR DRIVING RECOMMENDATIONS§
Alabama	6	No	Annually for 5 y from last seizure	No	Yes	No
Alaska	6	No	Individual	No	Yes	Yes
Arizona	3	Nocturnal, auras, AED revision	Individual	No	Yes	No
Arkansas	12	No	Individual	No	Yes	Yes
California	3, 6, or 12//	Nocturnal, breakthrough, AED revision	Individual	Yes	Yes	Yes
Colorado	//	No	Individual	No	Yes	No
Connecticut	3//	No	Individual	No	Yes	Yes
District of Columbia	12	Nocturnal, AED revision, and solitary seizure	1 y (until seizure free for 5 y)	No	Yes	Yes
Delaware	//	No	Individual	Yes	Yes	No
Florida	24//	Nocturnal (must supply EEG)	Individual	No	Yes	No
Georgia	12	First seizure, nocturnal	Individual	No	Yes	No
Hawaii	//	No	Individual	No	Yes	Yes
Idaho	//	MD recommendation	1 y (or semiannually)	No	Yes	No
Illinois	//	No	Individual	No	Yes	No
Indiana	//	No	Individual	No	Yes	Yes
Iowa	6	Nocturnal	6 mo, then at every renewal	No	Yes	No
Kansas	6	Nocturnal, solitary seizure	1 y (until seizure free for 3 y)	No	Yes	No
Kentucky	3	No	1 y	No	Yes	No
Louisiana	6	AED revision	Individual	No	No	No
Maine	3//	Seizure 'breakthrough'	Individual	No	Yes	No
Maryland	3	AED revision	Individual	No	Yes	No
Massachusetts	6//	MAB recommendation	Individual	No	Yes	Yes
Michigan	6	AED revision	Individual	No	Yes	Yes
Minnesota	6	Acute illness, AED revision, first seizure	Every 6 mo (until seizure free for 1 y)	No	Yes	No
Mississippi	12	No	Individual	No	No	No
Missouri	6	MD recommendation	Individual	No	No	No
Montana	//	No	No (MVA may require)	No	Yes	No
Nebraska	3	No	No	No	Yes	Yes

(continued)

TABLE 58-1 (continued)

STATE	LEGAL SEIZURE-FREE RESTRICTION (MO)	RARE EXCEPTIONS TO SEIZURE-FREE INTERVAL BASED ON MITIGATING FACTORS†	REQUIRED MVA MEDICAL REVIEW, TYPE OR INTERVAL‡	MANDATORY PHYSICIAN REPORTING	MVA LICENSE APPEAL	PHYSICIAN LIABLE FOR DRIVING RECOMMENDATIONS§
Nevada	3	MD recommendation	1 y (for 3 y)	Yes	Yes	Yes
New Hampshire	12//	MD recommendation	No	No	Yes	Yes
New Jersey	12	Neurologic MAB recommendation	Every 6 mo for 2 y	Yes	Yes	Yes
New Mexico	12//	Nocturnal	Individual	No	Yes	No
New York	12//	AED revision, MD recommendation	Individual	No	Yes	No
North Carolina	6-12//	Nocturnal, auras, AED revision	1 y	No	Yes	No
North Dakota	6//	No	1 y (at least 3 y)	No	Yes	No
Ohio	//	No	6 and 12 mo, then annually	No	Yes	No
Oklahoma	12	Nocturnal	MVA determines	No	Yes	No
Oregon	6//	Nocturnal, auras, AED revision, acute illness	Individual	Yes	Yes	Yes
Pennsylvania	6	Nocturnal, auras, AED revision, acute illness	Individual	Yes	Yes	No
Rhode Island	//	MAB recommendation	Yes	No	Yes	No
South Carolina	6	No	6 mo, then 3 y annually	No	Yes	No
South Dakota	12//	No	Every 6 mo (until seizure free)	No	Yes	Yes
Tennessee	6	No	At discretion of MAB	No	Yes	Yes
Texas	6	AED revision	1 y	No	Yes	No
Utah	3//	Yes	6 mo (until seizure free for 1 y)	No	Yes	No
Vermont	//	No	Individual	Yes	Yes	Yes
Virginia	6	Nocturnal, auras, AED revision, acute illness	Individual	No	Yes	No
Washington	6	MD recommendation	Individual	No	Yes	Yes
West Virginia	12	Nocturnal, auras, AED revision, acute illness	Individual	No	Yes	No
Wisconsin	3	No	6 mo for 2 y	No	Yes	No
Wyoming	3	Nocturnal	1 y	No	Yes	Yes

\*AED = antiepileptic drug; MAB = medical advisory board; MD = medical doctor; MVA = motor vehicle agency.

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†Mitigating factors considered in permitting some patients to drive despite less than minimum seizure-free period: auras, nocturnal seizures only, seizure breakthrough during physician-directed AED change, solitary or first seizure, MD or MAB recommendation.

‡Individual = MVA medical review conducted on a case-by-case basis.

§No = physician legally immune or indemnified; Yes = physician possibly liable for driving recommendation.

//Seizure-free restriction frequently adjusted by MVA MAB and treating physicians (Table 58-2).

**TABLE 58-2**  
**Summary of Driving Regulations in States with Flexible Driving Restrictions for Patients with Epilepsy\***

STATE	FLEXIBLE DRIVING RESTRICTIONS
California	6 mo seizure free; 3 mo if seizure occurs during physician-directed AED reduction or if previously seizure free 6 mo; 12 mo if repetitive seizure (several in 1–2 mo) after 6-12 mo seizure free
Colorado	Treating physician determines; 2-y restriction if not under physician's care
Connecticut	Minimum 3 mo seizure free; MAB and treating physician determine; 6 mo without recommendation
Delaware	Treating physician determines; must have been under physician's care for 3 mo
Florida	MAB usually shortens seizure-free period from 24 mo to 6 mo if under adequate medical treatment
Hawaii	MAB determines; usually 6 mo seizure free; treating physician indicates stable prognosis
Idaho	Treating physician recommends
Illinois	MAB determines; treating physician certifies patient is safe to drive; usually require 6 mo seizure free
Indiana	Treating physician determines; 12 mo seizure-free restriction without physician recommendation
Maine	Functional ability profile: driving generally permitted if >3 mo seizure free or 2 yr seizure free and off AED >3 mo
Massachusetts	6 mo seizure free; MAB may reduce interval if recommended by treating physician; MAB may increase seizure-free restriction
Montana	Treating physician recommends; must attest condition stable and would not interfere with safe driving
New Hampshire	12 mo seizure free; MVA frequently shortens interval on recommendation of treating physician
New Mexico	12 mo seizure free; MVA frequently shortens to 6 mo
New York	12 mo seizure free; MVA frequently shortens to 6 mo based on recommendation of treating physician
North Carolina	6-12 mo seizure free; determined by medical advisor
North Dakota	6 mo seizure free; temporary license for commuting to work or school frequently authorized by MAB if >3 mo seizure free with recommendation from treating physician
Ohio	Treating physician recommends
Oregon	6 mo seizure free usual; shorter intervals considered on recommendation of treating physician
Rhode Island	MAB determines
South Dakota	12 mo seizure free; MAB may give temporary license earlier with 6-mo reviews if physician verifies patient's statement that seizures are under control
Utah	Functional profile and treating physician recommendation (commonly 3 mo seizure free); may recommend limited driving (<40 mph, local roads, daytime only)
Vermont	MAB determines; usually 6 mo seizure free

\*AED = antiepileptic drug; MAB = medical advisory board; MVA = motor vehicle agency. Reprinted with permission from Krauss GL, Ampaw L, Krumholz A (28).

drive safely and in communicating his/her opinion to the individual with brain injury, family members and/or significant other. A tabular presentation (see Table 58-3) may increase the likelihood that the basis for the physician's opinion is understood. In this assessment, the less obvious impairments which fall into the categories of efficiency and accuracy of information acquisition and processing, multi-tasking, problem-solving ability, response to simultaneous stimuli and a rapidly changing environment, as well as judgment, self-awareness, impulse control, and emotional status, are taken into account. Each observed quality is rated "normal," "sub-normal" (an abnormality is detected, but is considered acceptable for driving), or "impaired" (representing potential interference with safe driving). The logic of this assessment is that it allows for the recognition of some impairments for which compensatory actions may be possible, while an

abundance of "sub-normal" findings, or a single "impaired" finding, would indicate that the physician should intercede to guard against the individual driving unless/until these component abilities recover adequately.

Schultheis, Hillary and Chute (34) compared the Neurocognitive Driving Test (NDT), a computer-based driving assessment tool, with a comprehensive hospital-based driver's evaluation of individuals with acquired brain injury (ABI). Participants included 15 adults with ABI and 15 matched healthy control (HC) participants. A significant relationship was found between the NDT and the comprehensive driving evaluation, and confirmed the value of the NDT in discriminating between the individuals who passed the comprehensive, hospital-based driving evaluation and those who failed. Additional research was recommended with larger sample sizes as was the inclusion of neuropsychological measures and



**TABLE 58-3**  
**Clinical Driving Assessment**

Name _____		Date _____	
Physician Evaluating: _____			
<input type="checkbox"/> Normal	(no abnormality detected)		
<input type="checkbox"/> Sub-normal	(an abnormality is detected, but considered acceptable for driving)		
<input type="checkbox"/> Impaired	(feature is present and represents a potential interference with safe driving)		
<b>Alertness and attention:</b>			
Level of alertness	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
Sustained attention, vigilance	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
<b>Primary sensation:</b>			
Visual acuity $\geq$ 20/40, reading	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
Hearing	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
<b>Acquisition of visual information:</b>			
Functional visual field	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
Eye movement	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
Obligatory head use in gaze	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
<b>Processing of visual information:</b>			
Information processing ability	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
Visual-spatial functioning	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
<b>Motor activation:</b>			
Foot strength	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
Praxis	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
Spasticity	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
Coordination	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
Intrusive involuntary movements of UE/LE	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
Ability to perform several motor functions at once	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
Other pertinent features of neurologic exam (specify)	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
<b>Motor response:</b>			
Response latency. Speed of reaction	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
Problem-solving ability	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
Response to simultaneous stimuli/changing environment	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
<b>Executive functions:</b>			
Judgment	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
Ability to predict/anticipate	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
Pertinent features on neuropsychological test (specify)	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
<b>Emotional status:</b>			
Impulse control	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
Degree of risk-taking	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
Suicidal depression or nihilism	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
Other pertinent features on psychiatric exam (specify)	<input type="checkbox"/> Normal	<input type="checkbox"/> Sub-normal	<input type="checkbox"/> Impaired
Ability to compensate for an identified difficulty		(clarify)	
Reliability in following a medical regimen		(comment)	
Functional assessment: ADL		(attach)	

TABLE 58-3 (continued)

**Overall Assessment and Disposition:**

- (1) No clinical impediment to driving is suspected.
- (2) Early or minor/acceptable difficulties are recognized. Reevaluate in six months. Patient able to compensate, adjust driving circumstances, or exercise adequate judgment to provide safety.
- (3) Safe driving capacity is not definite. Patient instructed to obtain special assessment, and instructed not to drive until that assessment is obtained. If patient cannot or does not comply, see (4).
- (4) Patient's driving constitutes a danger to public safety. Reporting may be obligatory in some states.

medical information in order to understand better the individual's cognitive impairments and the implications for driving performance.

Pietrapiana, Tamietto, Torrini et al. (35) described a study of 66 persons in Italy with severe traumatic brain injury, to explore the possibility of predicting post-injury fitness to drive. Predictor variables consisted of 16 measures representing demo/biographic, medicofunctional, neuropsychological and psychosocial domains. Driving outcomes were driving status (i.e., whether they returned to driving), driving safety (based on post-injury accidents) and driving violations. The findings were that the 50% resumed driving; the main difference was the shorter duration of coma in those individuals than the non-drivers. The variables that offered the best prediction of driving safety were the years post-injury, the number of pre-injury car accidents and driving violations, a pre-TBI risky-personality index, and pre-TBI risky-driving-style index. In combination, these four variables predicted 72.5% of the variance. The authors suggested that reports of pre-TBI histories be obtained from close relatives and/or significant others in making predictions about fitness to drive safely post-injury.

Although one's fitness to drive may be clearly evident in some cases, and the decision regarding driving is straightforward, in other cases one's fitness to drive may be marginal. In those cases, driver's training by an instructor with expertise in traumatic brain injury should be considered. The number of sessions would be determined based on the presenting issues, but should be provided at different times of the day and for sufficient lengths of time to be able to assess the possible effects of common sequelae such as fatigue and reduced physical and cognitive endurance on one's capacity to drive safely. Driver's training may also be recommended even in situations where the driver's evaluation clearly confirms one's capacity to drive, as a way for the individual, who may not have driven in quite some time post-injury, to have beneficial support and feedback while gradually returning to driving.

*The Use of Public Transportation or Paratransit Services*  
While many persons would assume that public transportation or specialized transportation (i.e., paratransit

services) offer persons with traumatic brain injuries a means to access the community, that is often not the reality. Physical, cognitive-communication, psychosocial and/or behavioral sequelae present enormous obstacles to the use of these systems. In rural areas, bus service may not be available or the nearest bus stop may be far enough away that non-drivers usually must walk to the bus stop. Persons with mobility impairments may be unable to walk that distance. In heavily trafficked areas, the individual may not be able to cross the street quickly enough to assure his or her safety. For individuals with cognitive impairments, inadequate time awareness and attentional deficits can lead to missing the bus, and poor problem-solving may result in impulsive behavior that puts the individual at risk.

Specialized transportation services are also often too complex for persons with traumatic brain injuries to utilize without assistance. Issues arise even when applying for such services since lack of awareness of one's disabilities may lead to inadequate information on application forms for eligibility, resulting in a decision that someone with no apparent mobility impairment does not require the services even when a significant cognitive impairment precludes his/her use of standard public transportation. If the individual is declared eligible for specialized services, cognitive-communication problems can undermine attempts to plan and schedule the trips. In particular, difficulty is encountered when transportation is not available at the time it is requested and the individual must consider, quickly, an alternative schedule. Moreover, when being picked up or dropped off by the transportation service, a 15-minute "window" is usual. Persons with attention deficits may become distracted and fail to be ready when the transporter does arrive. Many systems only allow this to happen twice before canceling one's eligibility for services. Trying to rectify some of these problems, the individual may attempt to contact the transportation service and encounter an automated telephone system with a menu of options that is too complicated for him or her to use successfully.

Cognitive rehabilitation therapy (offered by community re-entry programs) is strongly recommended to address these potential difficulties and should be

individually tailored to enable the individual to handle the cognitive demands of the transportation systems he or she will actually use. While cognitive rehabilitation can be aimed at remediating functions (e.g., improving attentional abilities as required to signal a bus to stop), the focus is typically on ways to compensate for lost or reduced abilities. For example, compensatory strategies may include the development of structured forms and a telephone script to use when calling to schedule a trip, visual cues or electronic devices (e.g., a watch alarm or timer) to remind the individual to prepare to leave the house at a specified time in order to reach the bus stop on time, role-playing of appropriate verbal exchanges with the bus driver and other passengers, etc. Accompanying the individual on bus rides initially should be part of the therapy process, followed by shadowing, and then independent trips with strategies for problem-solving situations if necessary. Sufficient repetition and rehearsal is essential to mastery of the skills required for use of public transportation.

### **THE ROLE OF THE PHYSICIAN IN COMMUNITY RE-ENTRY AND LONG-TERM CARE**

With respect to community re-entry programs and long-term care, the role of the physician can be discussed in relation to the responsibilities of medical management/medical consultation, and other professional activities, including education and training, research, and expert testimony. Discussion of these roles and responsibilities, in broad terms, follow.

#### **Medical Management/Medical Consultation**

Given the diversity in community integration programs, which may be residential or non-residential and based on multidisciplinary, interdisciplinary or transdisciplinary treatment models, the role of the physician will be dictated in large part by the specific focus of the program. Many community re-entry programs employ a medical director, on a full-time or part-time basis, whose responsibilities to the program include, in addition to patient care, functions such as strategic planning, program development, and program evaluation. In recent years, largely because of reductions in reimbursement and recognition of the growing extension of services into the community, many community re-entry programs have chosen to have physicians as consultants to these programs rather than employees. In either case, with respect to patient care, patients in some programs will have been discharged by their physician at an acute rehabilitation hospital (most often a psychiatrist, neurologist or neuropsychiatrist) to follow-up by their primary care or family physician. In other

cases, the hospital-based physician may continue to follow the patient post-discharge, for an indefinite period of time. Moreover, physicians in private practice may interface informally with community re-entry providers, providing medical management/consultation on an as-needed basis. The physician serves as a guiding resource to the program or to other providers (medical and non-medical) to define and solve problems of patients or clients (the term preferred in many community re-entry programs) as they arise, with special emphasis on the problems which arise as a direct result of the brain dysfunction and the problems of secondary disruptions that result.

Zasler (36) emphasized that directing a brain injury rehabilitation program requires a shift from the traditional medical model with a disease orientation, to a holistic treatment approach with a functional orientation. In particular, he pointed out that the physician must understand how an individual's functional capabilities can be compromised by neurological and/or musculoskeletal impairments, and what may cause functional decline at various points post-injury. The physician must also recognize when other medical and/or psychological issues and non-injury factors are not directly related to the traumatic brain injury but may compound the disability resulting from TBI and impede the brain injury rehabilitation process.

Physicians with expertise in brain injury rehabilitation also perform a vital role in relation to the individual's return to work following traumatic brain injury. The individual's physician may be asked to provide an opinion of the suitability of a particular job for an individual and to delineate any work restrictions and reasonable accommodations. The need for work restrictions and/or accommodations may be related to physical or cognitive impairments. In some federal agencies, such as the United States Department of Labor's Office of Workers' Compensation Programs (OWCP), a physician's review of the potential job is a mandated part of the reemployment process. Physicians may also be hired by OWCP to evaluate workers' compensation claimants and provide a second opinion or independent medical examination (IME).

Zasler (37) discussed the neurologic sequelae that frequently impede one's ability to return to work, which may include post-traumatic epilepsy, post-traumatic hydrocephalus, olfactory dysfunction, visual deficits, audiovestibular dysfunction, oropharyngeal dysfunction, communication deficits, bladder and/or bowel dysfunction, visuoperceptual deficits, neuropsychological issues, sexuality issues, neurophysical deficits, and orthopedic issues. There is clearly a role for the physician to help agency personnel, employers, vocational rehabilitation personnel, and case managers, as well as the individual with TBI and his or her family members and significant others, to understand the vocational implications of traumatic brain injury sequelae.

Breed, Flanagan and Watson (38) studied 258 individuals with traumatic brain injury and 65 individuals without any disability, to compare the frequency with which they reported health problems and to explore the effects of age and traumatic brain injury on one's perception of his/her health. They pointed out that the limited amount of information on long-term health problems following traumatic brain injury is surprising, given the "central regulatory role" of the brain in physiologic functioning. The results of the study revealed that the individuals with traumatic brain injury reported more endocrine, genitourinary and neurologic problems, and had more complaints of joint pain and sleep disorders. The differences were statistically significant.

With respect to medical management and/or medical consultation, it is important to recognize that community re-entry models of rehabilitation draw primarily upon origins within a variety of pragmatic rehabilitation-related disciplines (e.g., neuropsychology, psychology, occupational therapy, speech pathology) rather than on medical management based on pathophysiology, diagnosis, and prognosis. As in the case of individuals with developmental disabilities, the role of the physician evolved historically through a secondary and consultative role that was problem-oriented and typically specific to the subspecialty area of concern (for example, orthopedic interventions, epilepsy or hydrocephalus management, interventions for depression and psychosis, plastic surgery, visual and auditory/vestibular dysfunctions). Those needs were addressed *ad seriatum* in the consultants' offices without integration to the rehabilitation program as a whole. Moreover, cognitive rehabilitation programs in the United States, developed initially with a focus on traumatic brain injury, have more recently included persons with non-traumatic cerebral injuries: anoxia-hypoxia, encephalitis, stroke and aneurysmal subarachnoid hemorrhage, and survivors of brain tumor resection. The design of intervention by most of the rehabilitative team draws on the clinical features which these disorders have in common rather than drawing on their pathophysiological differences. At times the physician must introduce knowledge and direction leading to program design recognizing differences between types of brain injury.

An integrated approach to residential and outpatient care requires the physician to broaden the scope of practice, and requires an evolution in treatment paradigm within residential and long-term rehabilitation programs. In presenting a neurological model of rehabilitation, Mills and Alexander (39) and Mills, Cassidy, and Katz (40) have outlined the necessary components to achieve suitably informed integration of treatment within an interdisciplinary program that encompasses neuroscience and neuromedical diagnosis and intervention. Diagnosis in rehabilitation ideally addresses the mechanisms and

pathophysiology of impairment, and does not merely describe states or lists of functional impairments and disability. From a knowledge of pathophysiology, placed in the framework of neurological syndromes, predictions of improvement and outcome can be derived. That is, the physician is likely to bring to the treatment planning a critique which takes into account a more extensive knowledge of correlation between differentiated types of brain injury and consequent alterations of behavior. Moreover, the physician may articulate the rationale for a revision in expectations of recovery to higher or lower goal set-points, or a longer or shorter duration of treatment, to the treatment team who may define treatment needs in terms of observed functional deficits alone. The physician makes a pivotal contribution in defining the appropriate point of transition to long-term supervised situations for some, and in defining the need for redoubled rehabilitation-oriented efforts in others.

To some degree, all members of the rehabilitative team must be cognizant of premorbid personality and the premorbid endowment of abilities and limitations in defining an individual context for treatment planning. To this context is added behavioral analysis (which takes into account the environmental and interactive aspects of action) and symptom analysis (which generates hypotheses of involuntary and/or intentional generators of specific actions, expressions, or perceptions). The attribution of the meaning of both seemingly normal and seemingly disordered behaviors is drawn from these contexts, and placed in social, psychological, and biological frames of reference. In analyzing a given problematic behavior, understanding predisposing and precipitating factors, and the patient's manifest adaptive capacity, will be essential. The capacity of the individual with traumatic brain injury to adapt to his/her circumstances may reflect such factors as misperception, memory impairment, mental inflexibility, impulsivity, or hyper-reactivity. The physician or other professional who imports knowledge of mechanisms operant within specific neurological impairments will add an additional vital component. For example, a mechanistic view isolates perceptual errors, attribution errors, disconnection errors, overgeneralization errors, encoding vs. decoding errors in memory, and affect regulation vs. disinhibition errors. When grounded in a knowledge of the potentially reversible and potentially irreversible aspects of the brain injury, the rehabilitation strategy is transformed and redirected optimally. The presumed "natural history" of the disorder is then opened to interventions targeted to critical components.

In the modern era, the physician brings to the treatment team a perspective based on knowledge and practice of emerging neurochemistry, neurophysiology, functional neuroimaging, and cognitive neuroscience. These areas represented by the physician include psychopharmacology, cognitive-enhancing treatment, neuro-protective

treatments, techniques of physiologic neurorehabilitation, and biomechanical interface. In addition, there are rapidly developing areas of study in neuroplasticity, intracerebral transplantation and regeneration, and hormonal and neurochemical aspects of brain injury and recovery. Many of these issues have been introduced in other chapters of this book.

In the phases of community re-entry, the opportunity arises for the physician to address components of the disordered behavior with a rapidly expanding repertoire of agents. Focusing on the neuropsychiatric and neurobehavioral domains in particular, the components which may yield to pharmacological intervention include inattention, states of hyper- or hypoarousal, depression, mood cycling or lability, aggression, obsessiveness and rigid inflexibility, sleep cycle disturbances and daytime somnolence and/or fatigability, anxiety states (including posttraumatic stress disorder), pseudobulbar incontinence of emotional expression, hypersexuality or sexual dysfunction, psychosis (delusions, hallucinations), states of apathy, abulia, or failure of motivation and initiative. This is not an exhaustive list. At the same time, it is often the better strategy to integrate such interventions with non-pharmacological modalities, such as psychological support, cognitive rehabilitation therapy, structuring of routines, and education.

At present, many of the newer or experimental modalities of intervention are currently confined to the specialized outpatient clinics at university settings or research institutes, but it will be appropriate for the physician consulting in the community re-entry setting, in particular, to import these new modalities of treatment into the care of the individuals who are far into their post-acute recovery. In the future, rehabilitation may also include implantation of augmenting systems, for example, sensory devices for augmenting hearing and vision. At the present time, the physician is the representative of medical vigilance for such late complications as hydrocephalus, shunt failures, seizures, infections, endocrine disorders, and spasticity, as well as vigilance for adverse complications attributable to medications (SIADH, thrombocytopenia, extrapyramidal movement disorders, psychotoxic adverse side effects, and sedation being particularly common examples). In the population of individuals with traumatic brain injury, drug and alcohol abuse may be demographically over-represented. Accordingly, the physician's vigilance must extend to concerns over hepatitis, drug induced vasculitis, HIV infection, syphilis, tuberculosis, and vigilance for ongoing drug and alcohol abuse, including agents which may advance the degree of brain injury during the period of rehabilitation (toluene inhalation, and "recreational" psychostimulant abuse, for example).

In addition, non-traumatic factors such as late post radiation vasculopathy (in brain tumor survivors) and

anoxic encephalopathy may also be present, the latter adding to impairments in movement (cerebellum and basal ganglia), perception (visual cortex), and memory (hippocampus), in addition to the above. (Discussion of the diagnosis and management of late complications of traumatic brain injury is found in chapter XX of this book, by Long.) The cumulative effects of neurologic aging, and the superimposed impairment of acquired brain neurodegenerative diseases in elderly persons, will also occur in those injured by trauma, and will require a refreshing of medical differential diagnosis when a progressive worsening of the pattern of impairments is detected. By far, the most prevalent late complications are those which fall into the neurobehavioral and neuropsychiatric domain, which are closely linked with the nature of the individual's emotional and neurocognitive deficits.

Structures of the brain which are known to be disproportionately vulnerable in brain trauma include the frontal and temporal lobes, but also the amygdala, hippocampus and basal ganglia. Late neuropsychiatric complications are at least equally prevalent though less well localized, and include depression, psychosis, a spectrum of disinhibited and unrealistic behaviors, and a persisting failure of insight, self-observation, or initiative. These represent disruption of the interface between the individual with brain injury and the environment which, at times by analogy or by comparison to recognized neurological and psychiatric syndromes, benefits from a medical understanding or intervention. The involvement of neurology, neuropsychology, and psychiatry in the understanding of the behavioral consequences which are intrinsic to these lesions, while built on a long history of the clinical pathological correlation of discrete lesions, has enjoyed an ascendance only in the last few decades, coincident with the emergence of the bridging subspecialties of behavioral neurology and neuropsychiatry.

Psychiatry, while historically not as often relying on clinical-pathological correlation, has allusion to a nosology of discrete syndromes which serve as reference points for intervention. The knowledge of the constellations of impairments which follow typically from traumatic brain injury should be known to any physician involved in the care of these individuals, including the broad range of other specialists and primary physicians.

### **Determining the Need for and Choice of Community-Based Treatment**

After being discharged from the acute and subacute phases of rehabilitation, the status of treatment goals will determine the setting in which further recovery optimally will take place. Outpatient treatment and direct community re-entry will be possible if the individual with TBI has sufficient self-awareness of the need for it, and if outpatient resources are available to address persisting cognitive,

behavioral, emotional, vocational, and physical needs. If self-awareness is sufficiently impaired to result in unsafe or disruptive behavior, the consideration for residential community treatment will be stronger.

Circumstances which may prompt a referral to a residential or nonresidential community re-entry program for persons with brain injuries include, but are not limited to, the following:

1) When community re-entry programs can provide essential, ecologically-valid observations and treatment that cannot be provided otherwise. Treatment rendered in a clinic, facility or office setting may not yield a clear picture of the sources of failure to function adequately. The importance of gaining a better understanding of the individual's needs is underscored when the individual is caught in a cascade or vicious cycle of repeated failures to function adequately and requires external reinforcement of adaptive and compensatory strategies, and/or continual feedback.

2) When intervention is required because of failed executive functioning. This circumstance may become apparent in relation to individuals who attempt living on their own following traumatic brain injury but who are unable to resume functioning at, or close to, their pre-injury level. Common problems for those individuals include inability to follow a prescribed medication regimen, to manage family, financial or personal responsibilities, or to maintain an environment conducive to satisfactory functioning. Crises of disorganization can result, exemplified by hoarding of possessions or accumulation of items/objects, leading to overwhelming clutter and chaos.

3) When the individual is unable to establish functional routines as needed to accomplish activities of daily living. Sequelae of traumatic brain injury may include memory problems, inadequate planning and organizing, difficulty making decisions and impaired ability to initiate purposeful activity, contributing to the inability to carry out daily routines. Other variables compromising one's ability to establish and maintain a productive daily activity pattern include apathy syndrome, severe obsessive disorder (whose rituals or unresolvable obsessions create "paralysis" of activity), depression, and anxiety. There may be repeated failures to resume work, school or social/leisure activity.

4) When outpatient programs are not available (for reasons of lack of funding, distance, or other reasons) or are not intensive enough to meet the individual's needs. This circumstance may be particularly problematic if the individual's family is unable to provide adequate support for, or reinforcement of, treatment interventions and when inadequate daily structure leads to maladaptive behavior.

5) When continued supervision is necessary. Once individuals are discharged home, other family members often anticipate they will be able to resume their usual roles (e.g., return to work) and do not fully appreciate the

need for supervision that may be required by the individual with traumatic brain injury. Potential problems when adequate supervision is not provided include the use of alcohol or drugs, frontal syndrome with impulsivity and poor judgment, aggressive or disinhibited behavior, and frontal syndromes with anosognosia. Of paramount importance is the safety and well-being of the individual with traumatic brain injury and his/her family members. For example, memory problems may result in the individual forgetting to turn off the stove or oven, increasing the risk of fire. Fatigue is also common following traumatic brain injury and may result in the individual falling asleep while smoking. These possible scenarios underscore the need for supervision.

When the rehabilitative phase of post-TBI care yields to chronic maintenance or "custodial care," the physician's role remains vital. A number of factors, both physiological and psychological, may intrude and erode further the individual's quality of life and access to optimal level of functioning. It is also true that chronicity does not preclude the possibility of treatment targets that, when addressed, may improve function in the client who is many years beyond the scope of brain tissue recovery.

### **Other Physician Roles in Community Re-entry**

*Education and Training* In patient care settings, education and training by the physician (often in collaboration with other professionals) may be directed to family or caretaking staff, to the programmatic design staff and/or to the patient himself or herself. When providing education to the individual with traumatic brain injury, the physician will attempt to help the individual understand the commonalities that persist despite cultural differences and, at the same time, represent the essential voice of culture in steering the rebuilding of self. The physician can be called on to recognize, or ideally to teach others to recognize, physiological disorders which mimic psychological disturbances. For example, a disorder of initiation, motivation, or "apathy" may arise from brain injury and may mimic amotivational or apathetic mood states. Dysfunction of cortical-subcortical circuits are particularly implicated in such amotivational states, including the medial prefrontal area, anterior cingulum, nucleus accumbens, ventral pallidum or medial dorsal thalamus. It is essential that the treatment providers understand the difference, in order to select and render appropriate treatment methods. To assure optimal management of the patient, the treatment team must understand the pathophysiology of symptoms and signs of a given neurological disorder, and the natural history of both the disease and the impairments. When directing the treatment, the physician must assure that the team members understand the patient's impairment(s), diagnosis

and prognosis, and how to implement the interdisciplinary treatment.

Mills and Alexander (41) identified four essential educational components for every team member: 1) the neurological diseases they will treat; 2) goal-setting and plan development for patients with complicated cognitive problems; 3) appreciation of the treatment outside his/her own specialty; and 4) development and use of cost-effective, affordable approaches to assessment and treatment.

Continuing education and training of other physicians and nonmedical personnel will also help to increase understanding of the needs of persons with traumatic brain injury. Conferences sponsored by professional associations are a frequent venue for such offerings. Because of the multidisciplinary nature of the field of rehabilitation, the American Congress of Rehabilitation Medicine ([www.acrm.org](http://www.acrm.org)) and the American Society for Neurorehabilitation ([www.asnr.com](http://www.asnr.com)) are particularly relevant.

*Research* The National Institute on Disability and Rehabilitation Research (NIDRR), United States Department of Education, has been funding projects in the area of community integration through TBI Model System grants and Rehabilitation Research and Training Centers, which should provide valuable information to enhance understanding of the benefits of such programs, and opportunities for physicians to pursue research interests.

*Expert Testimony* The physician may be called upon for a variety of official tasks. He or she will be called upon to mediate in medicolegal issues (e.g., designation of payee for entitlements, statements of capacity/competence, assessment for guardianship proceedings, driving licensure, designation of impairment for professional work, or letters of medical necessity) and may also provide expert testimony in personal injury cases. See Chapter 62 by Cantor on medicolegal aspects of traumatic brain injury and Chapter 63 by Ameis et al. on ethical issues in clinicolegal practice.

Manifestations of frontal dysfunction, which pervasively undermine normal adaptations to social environments, are difficult to represent to the legal system (42, 43). The physician may be called upon to justify continued compensation under auto insurance policies (e.g., personal injury protection [PIP] or workers' compensation policies). In the current era, the precertification of treatments may require the physician to act as advocate, at times in opposition to third party payers who would profit by nihilism.

### Conclusion

There has been rapid growth in community re-entry services and long-term care for individuals with traumatic brain injury, spawned by greater understanding of their needs at this point in the rehabilitation process and augmented by legislative and managed care initiatives resulting in

shorter hospital stays and earlier return to the community. While the methodological problems inherent in conducting empirical studies at this point, with such a highly heterogeneous population and extensive array of services, have resulted in limited scientific evidence of the efficacy of these programs and services, their value to the individual and his/her family cannot be questioned. Findings of studies that have been conducted and anecdotal reports support the value of these services in improving the functional outcomes and enhancing the quality of life for individuals with traumatic brain injury.

Services and supports at this point in the rehabilitation process are typically provided by nonmedical as well as medical personnel. There continues to be a vital role for the physician in relation to medical management and consultation as well as in relation to education, training and research.

It is through the familiarity with neurobehavioral constellations (which can be interpreted to the injured individual himself or herself and to the involved family) that the physician's involvement may impact uniquely upon rebuilding of personhood and the integrity of self, a goal of intervention distinct from, but no less valuable than, the more narrow focus of remission of medical problems. The concept of self has a grounding presence in the neurorehabilitation of those in whom the cerebral substrate of self has been undermined. Kircher (44) conceptualized the self as the sense of being a whole person constant over time but different from others, and the center of all our experience. A challenge, both cognitive and emotional, is frequently placed before the individual with brain injury to synthesize and evolve a novel posture from which to carry his or her transformed life forward. At times this new synthesis must encounter or master social developmental issues which may have, or may not have, been mastered prior to trauma, and frequently this new synthesis involves great losses or compromises of deeply set life goals and pre-morbid self-definitions. The brain's impairments may interfere with the adaptation, reframing, or flexibility, which would be required to escape a negative self-definition of incompetence, disappointment, or abandoned aspiration in an individual whose mental repertoire and capacity is forever altered. The physician may offer the important contribution to that individual of informed wisdom, both hopeful and realistic, about the brain's potential, and offer a continuing and long-term commitment to the individual's progress, even as that person shifts from setting to setting, and from one challenge to the next.

### Note

*National Directory of Brain Injury Rehabilitation Services 2005 Edition*, Brain Injury Association of America, Inc., McLean, VA, 2005. This directory is published annually and includes listings of types of brain injury programs

and service specialties, state and national resources, and information about military/veterans services through the Defense and Veterans Head Injury Program. Also included are explanations of common abbreviations in the field of brain injury rehabilitation as well as the Rancho Los Amigos Levels of Cognitive Functioning Scale and the Glasgow Coma Scale (GCS). In the 2005 edition, Appendix A consists of a guide to selecting and monitoring brain injury rehabilitation services, and Appendix B contains a glossary and definitions of commonly used terms. The directory can be purchased by calling the Brain Injury Association of American at 1-800-444-6443 or accessing the association's website (www.biausa.org).

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# 59

## The Treatment of Substance Abuse in Persons with TBI

*John D. Corrigan*

### **THE TREATMENT OF ALCOHOL AND OTHER DRUG ABUSE IN PERSONS WITH TBI**

Clinicians working with people who have incurred a traumatic brain injury (TBI) cannot avoid the issue of alcohol and other drug use. Whether consumption of these substances contributed to the cause of injury, or their use after injury places the individual at risk for medical complications, alcohol and other drug use must be addressed with adolescents and adults in order to preserve the benefits of rehabilitation. In addition to medical complications, substance abuse also limits outcomes by undermining environmental supports such as familial care or access to services. Indeed, alcohol and other drugs may be so detrimental to recovery of function and lifestyle and, in aggregate, to the case that can be made for the benefit to society of rehabilitation services, that it would be short-sighted not to do all we can to minimize their negative effects.

This chapter provides a review of current research on TBI and the use of alcohol and other drugs. There is far greater information describing this problem and its scope than there is research on treatment approaches to ameliorate use-related disorders. Studies of the risks of substance abuse after TBI are discussed, including who is at risk. A review of interventions and treatment approaches that have specifically addressed substance use following TBI precedes explication of a theoretical

model for the development of interventions to treat substance use disorders following TBI. Use of this model is intended to better focus both research and program development.

### **WHAT ARE THE RISKS OF SUBSTANCE USE AFTER TBI?**

Persons with TBI and substance abuse problems are less likely to be working (1–3), have lower subjective well-being (4, 5), increased likelihood of suicide (6) and are at greater risk for seizure (7). There is also evidence from studies of incarcerated populations that the increased risk for aggressive behavior after TBI is further exacerbated by substance abuse. In addition to these psychosocial consequences, several studies have found an additive effect of negative consequences for both brain structure and function (8, 9).

### **Psychosocial Consequences**

Numerous studies have observed that substance use problems preceding injury are often a significant predictor of post-injury unemployment. MacMillan, Hart, Martelli and Zasler (3) studied 45 adults two years after moderate or severe TBI. They hypothesized that severity of

premorbid psychiatric and substance use disorders, as well as less social support following injury, would be associated with poorer post-injury employment, independent living and neurobehavioral symptom manifestation. They found that both pre-injury psychiatric and substance abuse histories predicted a lower likelihood of employment and that pre-injury substance abuse also was associated with less independence in living situation. Sherer, Bergloff, High, and Nick (2) studied 76 persons with moderate or severe TBI who received services through a specialized day treatment program. Employment status three months following discharge from this program was assessed, on average, two years post-injury. Predictors of employment status included severity of injury, premorbid education, pre-injury substance abuse, and need for physical, cognitive and behavioral supervision at discharge from acute rehabilitation. Multiple logistic regressions revealed that only level of pre-injury substance use was predictive of later productivity. Subjects with no history of pre-injury substance abuse were more than eight times as likely to be employed at follow-up.

Bogner and colleagues (4) investigated the relative contribution of substance abuse and violent injury etiology in a sample of 351 consecutive admissions for acute brain injury rehabilitation. At one year following injury prior history of substance use disorder was a significant predictor of post-injury employment, as were age, pre-injury employment and cognitive function at rehabilitation discharge. Despite the consistent finding that pre-injury substance abuse is associated with post-injury unemployment, the relationship with post-injury use may be more complex. Sander, Kreutzer and Fernandez (10) found that employed persons who had incurred moderate or severe TBI and were on the average 16 months post-injury reported consuming greater amounts of alcohol than similar subjects who were unemployed. This finding may be consistent with clinical observations that return to work can be a trigger for substance use because of having financial resources to purchase alcohol or other drugs, as well as increased stressors arising from the work environment.

Corrigan and colleagues (5) reported that a prior history of substance use disorder was highly associated with life satisfaction both one and two years after injury. At year one, prior substance abuse was the strongest independent predictor of life satisfaction and continued to be a significant predictor two years after injury, even after the effects of depressed mood, social integration and employment had been accounted for. Bogner and colleagues (4) considered whether life satisfaction was more affected by substance abuse history or violent injury etiology. As with employment, they found substance abuse history was the more important predictor, along with pre-injury employment and motor function at discharge.

In the general population there is a well documented relationship between depression and substance abuse (11),

and given the high rate of depression following TBI, the co-occurrence of depression and substance abuse would be expected in this population as well. Indeed, there has been some indication of an independent relationship between substance abuse and the likelihood of suicide following TBI. Teasdale and Engberg (6) examined suicide after TBI using the Danish population register for hospital admissions between 1979 and 1993. Standardized mortality ratios stratified by sex and age indicated the incidence of suicide relative to the general population was increased by 2.7 for concussions, 3.0 for cranial fractures and 4.1 for intracranial hemorrhage. When substance use diagnosis x TBI diagnosis was examined, standardized mortality ratios increased significantly. Silver, Kramer, Greenwald and Weissman (11) reported the relative risks of psychiatric problems for a randomly selected subgroup of the New Haven portion of the NIMH Epidemiologic Catchment Area study. TBI alone significantly increased the risk of suicide by an odds ratio of 5.7. After controlling for alcohol abuse and dependence, the likelihood of suicide attempt declined 4.5, suggesting that alcohol use accounted for approximately 20% of the risk of suicide after TBI.

Verma, Policherla and Buber (7) looked at the relationship between chronic abusers' withdrawal from alcohol and the occurrence of a seizure episode. They separated a sample of 54 adult male alcoholics who had experienced seizures into three groups—those for whom there was always a clear relationship between withdrawal and the seizure episode (the last drink occurring between 6 and 96 hours prior to seizure), those for whom some but not all seizure episodes were associated with withdrawal, and a third group in which none of the seizure episodes were associated with withdrawal. They found that a history of severe TBI preceding the onset of seizure disorder was present for none of those patients in the first group, approximately 40% of those in the second group, and more than 75% of those in the third. They concluded the lack of a constant relationship between alcohol withdrawal and seizure precipitation for the second and third groups appears to be a result of the higher incidence of prior TBI in those subjects, and that this relationship may account for the previously observed heterogeneity in the relationship between alcohol withdrawal and seizure episodes.

Finally, regarding substance abuse and poorer outcomes following TBI, there is mounting evidence of associations with aggression and criminal activity (12). Increased aggression following TBI has been reported in multiple studies (13–15). Persons with TBI are more likely to be involved with the criminal justice system (12, 16), and there is evidence of a high prevalence among prisoners. A sample of 1,000 consecutively admitted offenders to the Illinois state prison system found 25% had incurred at least one TBI (17). Of those reporting

TBI, approximately 20% indicated they experienced residual symptoms—most often problems with memory and learning, followed by changes in mood or behavior, seizures, and difficulties with balance and coordination. In a follow-up study Merbitz and colleagues (18) found that those inmates with a history of TBI had 50% more disciplinary tickets accrued per day of stay than a comparison group of inmates without.

In some studies of the prevalence of TBI and criminal activity and/or incarceration, there is additional evidence of a three-way co-occurrence of involvement with the criminal justice system, TBI and substance abuse. A study of medical center patients with TBI found those who had pre-injury histories of arrest were more likely to be males, with lower education, who were injured in assaults, and had a history of substance abuse (19). Barnfield and Leathem (20) studied persons with TBI and substance abuse problems in the New Zealand prison population. Their sample was considerably smaller than Morrell and colleagues', consisting of 118 prisoners who both were allowed to participate and agreed to do so. Subjects were asked to "estimate how many head injuries they had sustained, how each had occurred, and the duration of any loss of consciousness associated with each injury." Barnfield and Leathem used a combination of reported loss of consciousness and frequency of injuries to derive a categorization system for severity that classified each subject as having none, light, mild, moderate, or severe TBI. Half of their sample incurred a TBI that was mild or worse, with 17% reporting moderate or severe injuries. Inmates with mild or worse TBI were approximately 17% more likely to have severe substance use disorders.

Walker and colleagues (21) studied 652 male inmates in four Kentucky prisons. Subjects had used drugs at least three times during the year prior to incarceration, and had had at least two months outside of a controlled setting prior to being incarcerated. There were relatively equal proportions of inmates who were currently being treated for substance use disorder, had been previously treated but were not currently, and those who had never been treated. Subjects were asked to report prior histories of "head injury" caused by various etiologies. Within this sample, 32% reported no head injuries, 38% one head injury, and 30% more than one. Self-reported cognitive and behavioral issues in the 30 days prior to incarceration showed that inmates with head injuries were more likely to have experienced depression, suicidal ideation, and cognitive problems. Those inmates who reported multiple head injuries were also more likely to experience anxiety and violent thoughts. These differences were more pronounced when lifetime symptoms were reported. Subjects with TBI were more likely to have experienced hallucinations and have suicide attempts. Furthermore, for symptoms of depression there were significant differences

between those with just one head injury and those with multiple. A similar pattern was evident for problems of cognition. Subjects were also asked about lifetime health problems. While there were no differences in terms of urogenital, hepatic, or dental problems; there was a significant relationship between a prior history of TBI and respiratory, musculoskeletal, circulatory, gastrointestinal, neurologic, dermatologic, and otolaryngial problems. Problems with alcohol, other drugs, and mental health were significantly related to a history of TBI. For alcohol and mental health problems, those with multiple injuries had significantly greater problems than those with just one injury. These results accentuate those from other studies of prison populations that have found greater difficulties in cognitive processing, mental health disorders and violent behavior. This study also suggests that health problems related to multiple systems may be associated with a history of TBI.

### **The Effects on Brain Structure and Function**

Several studies have found that substance use disorders and TBI have a negative, additive effect on brain structure and function. Bigler and colleagues (9) reported results of quantitative magnetic resonance imaging (QMRI) for 99 adults with TBI and 197 without. Of the TBI subjects, 18 were identified as having a history of substance use disorder. All TBI subjects differed significantly from the non-injured controls for various indices of structural brain damage reflecting atrophy, including the ventricle to brain ratio (VBR). The TBI subjects with a history of substance use disorder showed even greater atrophy when compared to those TBI subjects without. However, a sub-group of the TBI patients without substance use history matched for initial Glasgow Coma Scale score did not show significantly different measures of cerebral atrophy from those with substance use disorders. While this may indicate that the effect was not additive, it is also possible that GCS scores for those with substance use disorders were artificially lowered by intoxication at the time of injury. Despite this bias toward the abusing group having potentially less severe injury than the group matched on GCS, the abusing group still had a higher VBR, though not statistically significant. A follow-up study by Barker and colleagues (22) that examined polysubstance abusers with and without TBI concluded that when the effects of TBI severity are controlled, the effects of substance abuse in combination with TBI resulted in greater brain atrophy than that observed with either substance abuse or TBI alone. In this study, neuropsychological test performance did not show a similar additive effect. The authors conclude that the neuropathological changes detected by QMRI may be more sensitive than neuropsychological performance.

The interaction of alcohol abuse and TBI was studied by Baguley and colleagues (8) using event related evoked potentials. Forty male subjects constituted four equal groups based on the presence or absence of TBI and history of heavy social drinking. Subjects with TBI had experienced a severe TBI one year or more before being evaluated. Heavy social drinking was determined by the Alcohol Use Disorders Identification Test (AUDIT, reference) and is often considered equivalent to a diagnosis of alcohol abuse. Neuropsychological testing was also performed. No significant differences in average age or neuropsychological performance were observed among the four groups defined by TBI and alcohol abuse, TBI or alcohol abuse, or neither. Both the N200 latency and P300 amplitude were impaired in persons with either alcohol abuse or non-drinking subjects with TBI when compared to the control subjects. Significant impairment was observed in subjects with both TBI and alcohol abuse. A similar relationship was not observed for neurologic processes resulting from less complex cognitive tasks. These authors concluded that heavy social drinking after TBI has a measurable impact on electrophysiological correlates of cognition. While two of these studies looking at brain structure and function did not find differences in neuropsychological performance among subjects, other studies have shown more definitive findings. Dikmen and colleagues (23) found that individuals with chronic alcohol use disorders had greater neuropsychological impairment immediately following injury and two years later.

### WHO IS AT RISK FOR POORER OUTCOMES?

Patients who are known to have been intoxicated at time of injury often receive the most scrutiny of their substance use. However, persons with prior histories of substance use disorders (who may or may not have been intoxicated at time of injury), and those who use excessively after injury (who may or may not have had a prior substance use disorder) may be at risk for the greatest functional impairment. There is considerable overlap among groups defined by intoxication at injury, prior history and post-injury abuse, though comprehensive epidemiologic data is lacking.

#### Intoxication at Time of Injury

A number of patients are intoxicated at the time of their TBI (24, 25). The only population-based estimate of occurrence of intoxication at the time of TBI comes from the Colorado TBI Surveillance Follow-up System (26). For persons 16 and older admitted to hospitals in Colorado with a diagnosis of TBI, 20.8% had a blood alcohol content tested above 80 mg/dL, the legal limit for

intoxication in Colorado. As Corrigan (24) has observed, there is a tendency for persons with TBI treated in rehabilitation to have more severe markers of substance use disorders, including intoxication at the time of injury. Based on 3,787 acute rehabilitation admissions included in the TBI Model Systems National Dataset, 37% had a blood alcohol content greater than or equal to 100 mg/dL, the legal limit in most states during the time these data were being collected (27). A consecutive sample of 356 patients admitted for acute rehabilitation on the Brain Injury Unit at the Ohio State University Medical Center, 25% were found to have blood alcohol content greater than 100 mg/dL. Those with positive toxicology screens for other drugs comprised 12% of the cohort. Because there is extensive overlap between those intoxicated due to alcohol and those due to other drugs, the percentage of patients intoxicated due to either was 32%. Estimating the rate of intoxication among persons with TBI from these few studies, for all patients hospitalized it would be reasonable to project that 20% to 30% will be high at the time of the injury. Among patients admitted for rehabilitation after TBI, the rate appears to be between 30% and 40%.

Corrigan (24) summarized reports from the research literature indicating that those acutely intoxicated were more likely to have more severe injuries, require intubation, develop pneumonia and have other forms of respiratory distress; manifest greater neurologic impairment at discharge, have longer agitation and lower cognitive function at acute hospital discharge, and require greater time from admission to rehabilitation. However, other studies that examined the effect of intoxication found no relationship to mortality and morbidity, and in some cases an inverse relationship. Even highly reliable indices of outcome such as neuropsychological effects have been found by some but not others. For instance, Kaplan and Corrigan (28) found that there was no difference in neuropsychological performance among those with and without acute intoxication. However, Tate and colleagues (29) concluded that after controlling for pre-injury history of alcohol abuse, alcohol intoxication at admission was predictive of poor delayed verbal memory, greater decrement in verbal memory over time, and poor visuo-spatial functioning. Tate's methodology controlled for prior history of abuse, which may account for this discrepancy in findings. The ambiguous findings regarding the consequences of intoxication also have been mirrored in results from animal models in which there have been studies showing both the deleterious effect of intoxication at time of injury (30) and a neuroprotective effect posited by Kelly and colleagues (31, 32). Whether there is a neuroprotective effect in humans for the presence of ethanol at the time of injury is beyond the scope of this chapter. However, the question cannot be easily extracted from determination of the effects of a prior history of substance use, which based on

clinical studies, appears to exert a greater impact on initial acuity and longer term outcomes.

### **Prior History of Substance Use Disorder**

A person's prior history of substance use disorder may be a more important risk factor for poorer outcomes than whether they were intoxicated at the time of injury. Corrigan (24) found that studies of the effect of a prior history of substance abuse were far less equivocal in finding immediate consequences than the studies of intoxication. Prior history was found to be associated with mortality, likelihood of mass lesions, poor Glasgow Outcome Score at discharge, and poorer neuropsychological performance at both one month and one year post-injury. Only one study found no differences between persons with and without a history of substance use disorders (33). In the only study that compared the relationship to outcome of both history and intoxication (34) significant effects on mortality and morbidity were found for a history but not intoxication. This greater likelihood of morbidity may have in part accounted for the observation that a greater proportion of persons with prior histories of substance use disorders are found in rehabilitation populations of persons treated for TBI when compared to those treated in trauma centers only (24).

The Colorado TBI Registry and Follow-up System reported that 10% of persons age 16 and older hospitalized in Colorado had been treated previously for substance abuse, and 17% had used an illicit drug in the 12 months preceding their injury (35). In both cases, males, those younger, and those with more severe initial Glasgow Coma Scale scores were more likely to manifest these conditions. There have been two epidemiologic studies suggesting the onset of substance abuse precedes the onset of TBI (36, 37). Fann and colleagues (36) conducted a case control study in a large staff model HMO and found that persons diagnosed with a substance abuse disorder in a given 12-month period had a 60% greater chance of incurring a TBI requiring hospitalization or treatment in an emergency department or physician office. Timonen and colleagues (37) examined the birth cohort of Northern Finland for indications of childhood TBI as a risk factor for development of psychiatric disorders, substance use disorders, or criminality. While TBI in childhood was found to be associated with certain psychiatric diagnoses and criminality, childhood injury did not appear to predict the occurrence of substance use disorders.

From studies that used a prospective method of detection to evaluate rehabilitation populations, Corrigan (24) concluded that approaching two-thirds of adolescents and adults treated in rehabilitation for TBI have prior histories of substance use disorders. Since that time, at least three studies have provided additional data about the frequency of a prior history of abuse and dependence

among rehabilitation patients. Corrigan and colleagues (38) analyzed the TBI Model System National Database for the rate of prior histories of problem use. Problem use was defined as either at-risk consumption of alcohol or use of an illicit drug. They found that 43% of subjects in the TBI Model Systems National Database had prior histories of at-risk alcohol use, 29% reported pre-injury use of illicit drugs, and 48% showed either levels of use pre-injury. In a prospective study of 356 consecutive admissions to acute rehabilitation at the OSU Medical Center, Corrigan and colleagues (39) reported that 54% were diagnosed as having pre-injury alcohol dependence or alcohol abuse, and 34% were diagnosed as having pre-injury abuse or dependence of other drugs. Given the high rate of co-occurrence of alcohol and other drug use disorders, 58% of the sample showed one or the other or both. Bombardier, Rimmel and Zintel (40) reported very similar results for 142 consecutive admissions to acute rehabilitation at the University of Washington. In this sample, 58% had active alcohol use problems (or worse), 39% had recently used illicit drugs, and 61% had either or both histories. The rates from these three sources suggest relatively consistent results in terms of the frequency of prior history of substance use disorder in persons receiving rehabilitation for TBI. Because the OSU and University of Washington studies used more thorough methods of detection, it would appear to estimate that as many as 60% of adolescents and adults treated in acute rehabilitation for TBI are problem drinkers or have diagnosable substance use disorders.

### **Use Following TBI**

The Colorado Follow Survey reported 10% of persons hospitalized with a TBI used an illicit drug in the first year after injury (35). Silver and colleagues (11) found that approximately 25% of a population-based sample of persons with TBI also had alcohol use disorders (versus 10% for those without TBI); and 11% had other drug use disorders (versus 5% without TBI). Like other patients hospitalized due to injury, persons with TBI consume less alcohol or other drug in the immediate post-injury period (41–44); however, there are also indications that a significant proportion return to pre-injury levels of use relatively quickly (44–46).

Horner and colleagues (47) reported results from the South Carolina Traumatic Brain Injury Surveillance and Follow-up Registry. One thousand, six hundred and six adults were interviewed by phone one year after hospitalization for TBI. Among other questions, alcohol use in the month prior to the interview was classified in to three levels: heavy, moderate, or abstinence/infrequent/light drinking. Of survey respondents 15% reported heavy drinking in the prior month, 14% a moderate level of drinking. Risk factors for heavy drinking included a

pre-injury history of substance abuse, a diagnosis of depression since the injury, better physical functioning, male gender, younger age, being uninsured or on Medicaid, and not being married. Similar patterns were evident for moderate levels of drinking. There was no association between post-injury drinking patterns and TBI severity.

Kreutzer and colleagues (48) first reported that persons with TBI consumed significantly more alcohol before their injuries than same-aged peers; but after injury reduced to comparable levels. Those authors questioned whether drinking as much as other young adults was appropriate for persons who had sustained significant TBI. Later data from the TBI Model Systems National Dataset indicated that significant individual changes occur in drinking patterns over the first four years after injury (49). Of particular interest was the number of subjects who were abstinent and infrequent drinkers at one year post-injury who had increased their consumption by the second year—almost 25% of this longitudinal sample increased alcohol use between the first and second years. Other drug use was not examined. Kreutzer, Witol and Marwitz (49) studied 87 16–20 year olds at an average of 8 months and 28 months post-injury. Before their injuries, 51% were moderate or heavy alcohol users. At 8 months, this proportion was halved with 25% reporting moderate and heavy drinking; however, by the second follow-up this proportion had increased to 35%. Illicit drug use appeared to follow a different pattern, with 29% reporting any use before injury, dropping to 6% and 8% at the first and second follow-ups, respectively. Corrigan, Smith-Knapp and Granger (46) found that substance abuse problems increased dramatically between the second and third year in a cross-sectional study of rehabilitation patients with TBI. Bombardier and colleagues (41) studied 197 adults hospitalized with TBI and found that 65% were moderate and heavy drinkers pre-injury, a proportion that declined to 41% one year after injury. When only heavy drinking and whether the subject experience functional problems as a result of alcohol use were included in a composite index, the pre-injury rate was 51%, while that for one year post-injury was 26%. This study may have been confounded by the sample composition (a disproportionate number of subjects with known risks for seizures) and the failure to include other drug use.

Finally, there is evidence that some proportion of persons with no pre-injury substance use problems develop them after. For instance, among clients with TBI admitted for substance abuse treatment after injury, approximately 20% of those who had abstained from alcohol or were infrequent drinkers pre-injury, became high volume users after (45). This rate may have been inflated by including clients whose TBI occurred in childhood. However, Bombardier (41) found that 15% of pre-injury abstinent and light drinkers were consuming moderate or heavy amounts

by one year post-injury. Neither study consider other drug abuse onset; however clinical experience suggests that some proportion of patients with TBI initiate other drug use to alleviate pain, depression or anxiety. More research on the onset of other drug use would clearly be useful.

### WHAT INTERVENTIONS WORK?

While descriptive information is beginning to accumulate about the scope and nature of substance use and TBI, research on interventions for this problem is almost nonexistent. The only randomized controlled trial was a test of methods for improving engagement in treatment (50). Quasi-experimental studies have provided modest support for the efficacy of motivational interviewing and case management, respectively. There is ample reason to suspect that persons with TBI present for treatment with characteristics unique enough that the effectiveness of proven substance abuse treatment approaches should be evaluated specifically in this population. The greater the cognitive and emotional sequela of the TBI, the more necessary this research becomes. The effectiveness of both pharmacologic and behavioral interventions is required.

There are approaches to treatment being developed for special populations within the substance abuse treatment field that merit further consideration for persons with TBI. For instance, several treatment models have been developed for persons with co-occurring substance abuse and mental illness (51). There are many parallels between these dually diagnosed clients and persons with TBI and substance use disorders. Both populations have cognitive and emotional sequela arising from their disorders; members of both groups report using for regulation of emotional symptoms; and both groups often have multiple other psychosocial needs (e.g., housing, finances, transportation) that arise from or are interdependent with their treatment needs. Techniques developed and lessons learned in the treatment of persons with substance abuse and mental illness may be a fruitful source of ideas for addressing the needs of persons with substance abuse and TBI.

### Intervention and Treatment of Substance Use Following TBI

Clinicians and researchers have repeatedly observed that cognitive and emotional impairments caused by brain injury present unique problems when addressing co-existing substance use disorders (52–54). While several models of how substance abuse treatment can be adapted to TBI rehabilitation were proposed in the past (52, 55), most presumed protracted inpatient or residential treatment that is no longer available to most persons with TBI. Bombardier and colleagues have promoted brief interventions based on motivational interviewing techniques for use

during acute rehabilitation (56, 57). Cox, Heinemann, and colleagues (58) found some support for the efficacy of Motivational Counseling based on a quasi-experimental design using a non-random comparison group. In contrast, Corrigan, Bogner, Lamb-Hart, Heinemann & Moore (50) found a brief motivational intervention did no better than an attention control condition in terms of engaging clients with TBI and substance use disorders in substance abuse treatment. In contrast, a financial incentive condition and a condition in which logistical barriers were systematically addressed both resulted in significantly better engagement than the motivational interviewing and attention control conditions. However, the very brief duration of the intervention, delivered via telephone, may have served to undermine the effectiveness of the motivational interviewing.

The only community-based model other than Cox, Heinemann and colleagues (58) Structured Motivational Counseling is the model proposed by Corrigan and colleagues (42, 59, 60). This model uses consumer and professional education, intensive case management, and inter-professional consultation to address substance use disorders in adults with TBI. Program evaluation data suggest significant differences in outcomes depending on whether discharge occurred before an eligible client could be engaged in treatment (eligible but untreated), after initiation of treatment but before treatment goals were met (premature termination) or upon mutual agreement with staff that goals had been met (treated). The Network's three programmatic outcomes (abstinence, return to work or school, and subjective well-being) assessed three months post-discharge are shown in Figure 59-1. The median length of stay for those discharged successfully is 2 years. As might be expected, drop-out is a significant problem in this model. Retrospective analysis of 1,000 consecutive referrals indicated that 66% of those eligible for treatment either are not engaged or drop out prematurely. Heinemann, Corrigan and Moore (60) used a quasi-experimental design to study initial progress in two programs using the model and a non-random, comparison group of persons with TBI and substance use

disorders who were not receiving treatment. Nine months after admission to treatment, actual use did not change for either the treatment or comparison groups; however life and family satisfaction were significantly better for the treated group. Program referral earlier after injury was associated with larger gains in physical well-being, employment and community integration. The authors concluded that change in substance use requires longer duration treatment, and also noted the challenge of premature termination. If a case management model is found to be an efficacious treatment approach for this population, its effectiveness would be improved by determining better methods to engage and retain clients in treatment.

There is also substantial evidence of the co-occurrence of TBI and substance use disorders in the caseloads of substance abuse treatment providers. Alterman and Tarter (61) found 53% of a sample of 76 male alcoholics had histories of TBI. Hillbom and Holm (62) observed that 38% of a sample of 157 alcoholics had a history of TBI with loss of consciousness or hospitalization. Malloy and colleagues (63) found 58% of a sample of 60 alcoholics had TBI marked by loss of consciousness, hospitalization, or major neurological change. In a more recent study Gordon and colleagues (64) reported finding 63% of 243 consecutive admissions to 13 publicly funded programs in upstate NY were positive for TBI, as were 48% of 404 clients screened in 12 facilities in New York City. Researchers at Ohio State University studied a sample of 119 clients receiving residential treatment, intensive outpatient or ambulatory detoxification in a publicly funded substance abuse facility (65). They found that 68% had at least one TBI with loss of consciousness  $\geq 5$  minutes or requiring Emergency Department care or hospitalization. Perhaps more remarkably, 35% the entire sample had at least one TBI with loss of consciousness of at least one hour or requiring hospitalization. Furthermore, 53% of the sample had at least one TBI from which symptoms persisted at the time of screening. This study also found that clients with substance dependence and TBI showed selected differences on tests of cognitive functioning and emotional control when compared to clients with substance dependence only.

When considered together, it appears justified to expect as much as half of clients in substance abuse treatment to have histories of TBI. Cognitive impairments arising from TBI may affect a person's learning style, making participation in didactic training and group interventions more difficult. Misinterpretation of attention or memory problems as resistance to treatment can undermine a treatment relationship. Damage to the frontal lobes affects executive thinking skills and promotes socially inappropriate behavior. It is easy to interpret these behaviors as intentionally disruptive, particularly when the individual with TBI shows no visible signs of disability (53).

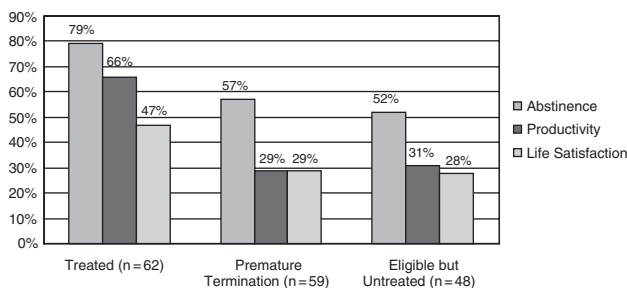


FIGURE 59-1

Outcomes at 3 months post-discharge for randomly selected, treated and untreated clients



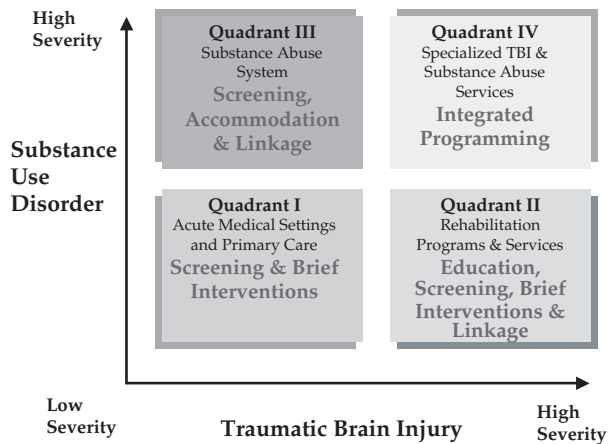


FIGURE 59-2

The four-quadrant model of interventions for substance abuse intervention

#### A 4-Quadrant Model of Substance Abuse Intervention

To help establish a context for a comprehensive research agenda, we have proposed a model for considering variations in the severity of these co-occurring conditions and the association with treatment venues and approaches. The starting point for the schema was borrowed from the literature on persons with co-occurring substance abuse and mental illness (51). As shown in Figure 59-2, persons with substance abuse and TBI are assumed to vary according to the severity of each condition. When mapped orthogonally, four quadrants are defined by high or low severity of each condition. While dichotomizing severity is relatively arbitrary, it proves useful in considering the service delivery systems where individuals are likely to be found. For instance, persons with low severity substance use disorders (e.g., high risk use or substance abuse) and low severity TBI are not found in treatment systems dedicated to substance abuse or TBI as often as they are found in primary care settings and treatment systems for injury (e.g., emergency departments or trauma centers). Only with more severe substance abuse or TBI, is a person likely to receive treatment in programs dedicated to chemical dependency or TBI, respectively. In our model, the co-occurrence of severe presentations of both conditions requires specialized treatment programs; however, given the essential absence of such services this quadrant of the model is mostly hypothetical.

Differences in the service delivery systems where individuals are most likely to be identified dictate different treatment approaches. For instance, in Quadrant I, the most effective interventions will need to be compact in order to accommodate the more pressing agenda of primary care or emergency treatment of an injury. Thus, screening and brief intervention are the most likely services to be provided. Indeed, there is a significant body of literature on

screening and brief interventions for both primary and emergent care (66). Similarly, quadrants II-IV dictate different service delivery opportunities, though in contrast to Quadrant I, there is very little research to guide clinical practice. We expect that an advantage of this model is that research questions can be generated specific to each of quadrants II-IV, and provide guidance both to clinical practice and the configuration of health care delivery systems.

#### Best Practice in Rehabilitation Settings

Though evidence for effective treatment is scant, the scope and nature of the problem requires that substance use be addressed in TBI rehabilitation. Corrigan, Bogner & Lamb-Hart (54) have suggested that all rehabilitation centers provide patient and family education, screening, and, for those at greater risk, referral to community resources. Education should be provided for all patients and families, independent of prior history. Although light or occasional alcohol use does not constitute a substance abuse problem in the general population of healthy adults, multiple factors necessitate different criteria for assessing substance use after TBI. There are several risk factors for development of substance use disorders, or complications accompanying them, applicable to the TBI patients:

- young age;
- high frequency of a prior history;
- unknowns regarding effect on the recovery process;
- decreased tolerance for any drugs;
- interaction with prescribed medications;
- potential to cause seizures;
- exacerbation of sequelae of brain injury; and
- the stresses of prolonged recovery from serious brain injury.

While a “safe” amount to drink for the general population of healthy adults can be recommended, risk factors associated with brain injury make it difficult to identify a level of consumption, other than abstinence, that is certain to not be detrimental. A palatable message for persons who have had a TBI is that no matter the extent of one’s use before an injury, the occurrence of TBI dictates a re-examination of health factors associated with any substance use. Thus, every patient, regardless the prior history or potential risk, should receive education regarding risks associated with substance use following TBI. The information provided should include the potential effects of alcohol and other drugs on recovery, detrimental impact on cognition and behavior, as well as health risks associated with substance use. Families also need this information, as well as additional suggestions for supporting behavior change. While education should be designed for all patients regardless of risk, it provides initial groundwork for those with prior substance use

disorders who need to reconsider their use after TBI. A consistent message about substance use after TBI provided by the entire rehabilitation team creates dissonance between the desire to use and the desire to achieve an optimum recovery. Subsequent referral for treatment is more likely to be successful if the individual is beginning to consider consequences of substance use.

Screening should be conducted during rehabilitation to determine which patients have prior histories of substance abuse or dependence, and thus require referral for on-going treatment. Laboratory tests for alcohol or other drugs are not adequate to determine which TBI patients' substance use is likely to interfere with their rehabilitation and long-term recovery. The presence or absence of drugs at any given point in time cannot confirm or rule out pre-existing substance use disorders, or the potential for them to emerge after discharge. Tests of liver function will be prone to false negatives. A prior history of substance use disorder is best determined from information provided by the patient or a knowledgeable family member. There are standardized measures for inquiring about alcohol abuse and dependence (e.g., the Brief Michigan Alcohol Screening Test (67), the AUDIT (68) or the CAGE (69)), as well as illicit drug use (the DAST (70), or the SSI (71)). However, standardized instruments may be compromised by cognitive impairments common in the acute phase of recovery. A sensitively conducted interview may be the most flexible way of gaining the information necessary to make a determination of prior history and future risk; however, a staff member must be adequately trained and comfortable with the subject matter and method.

Those patients at greater risk for substance abuse after discharge need additional attention. If specialized services are not available through the TBI rehabilitation program, then a referral to community resources needs to be made. Referral is not just providing a name and phone number, it is an intervention. Every TBI rehabilitation program should have a method for making a referral in such a way that patients will find the community resource accessible, acceptable, and useful. The program should develop a referral network of providers who, through experience and training, have some understanding of the unique issues of TBI. Community providers can be most effective when they are adequately prepared for the client. The rehabilitation program should provide educational materials or in-service training regarding TBI in general, as well as common characteristics of persons who may be referred. Cultural congruence should play a role in choosing an appropriate resource, whether AA group, individual counselor, or culturally-specific treatment programs (if available) in the home community. When possible, staff should visit referral sources to gain a better appreciation of the program and facility. For instance, will there be issues of physical, cognitive or financial access? Patients and family members should be prepared for the first meeting with a

provider in order to increase the likelihood that they will accept the services offered. Furthermore, the rehabilitation program's responsibility for referral is not complete until it is determined that at least an initial contact occurred. Better yet, follow-up communication with either the person served or the provider should be undertaken to ascertain that premature termination did not result.

Ultimately, the problem of substance abuse affects all aspects of a person's recovery and all staff members should be a part of the education, screening and referral process. Attention should be given to the attitudes, beliefs and knowledge of the entire professional, if not non-professional, treatment staff. A formal policy should be developed to identify which team members have responsibility for conducting patient and family education, compiling information regarding alcohol and other drug history and risk factors, and making referrals to outside resources. All treatment professionals should support the process, as relevant information or insights may come from statements expressed spontaneously during any staff members' interactions. Substance abuse is a complex behavior, and changing it is difficult. Though there are many issues to confront during rehabilitation, there is a unique opportunity to address substance use and abuse. The consequences of a TBI may cause a patient to question risky behavior. Detoxification has occurred by the time rehabilitation commences. Family members may be more willing to intervene after experiencing the emotional trauma of serious injury to a loved one. Acute rehabilitation following injury is an opportunity for substance abuse intervention that should not be squandered.

## CONCLUSIONS

Rehabilitation professionals lack the empirically based evidence for treatment of persons who incur a TBI and experience substance use disorders. There is considerable need for research to determine the extent to which interventions found effective with the general population are also effective with this group of patients. The anecdotal clinical experience from substance abuse treatment is that many approaches are either not effective or have to be substantially adapted to address persons with TBI. In addition to research on interventions, the field would benefit from additional epidemiologic data about who is at risk for substance use and why. Some patients significantly reduce use after injury while others start or resume. Furthermore, it would be very useful to know how neurobehavioral impairments that result from TBI differ from those that arise from chronic substance use, and whether and how such differences affect treatment.

For our health care systems to be more capable of addressing this population, we need research based recommendations as to what methods of screening for substance

use disorders are the most effective in persons with TBI. Similarly, how do neurobehavioral impairments due to TBI interact or moderate the efficacy of brief interventions for substance use. Within the substance abuse system, we need to know the most effective methods for screening for TBI and to have research based recommendations for how treatment can be adapted and impairments can be accommodated. As suggested by the Four Quadrant Model, we are sorely in need of models for integrated treatment of those individuals with more severe manifestations of both TBI and substance use disorders. Assuming effective models can be identified, we then need to determine how treatment can be made widely available to persons needing this level of care.

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# 60

## A Cognitive-Behavioral Intervention for Family Members of Persons with TBI

*Angelle M. Sander*

**T**he current Zeitgeist in the field of rehabilitation emphasizes the role of the environment in the ability of persons with impairments to participate fully in all societal roles and to integrate into their communities (1–4). The environmental context can foster the full integration of persons into the community or can provide barriers.

With the increasing emphasis on the importance of the environment, the role of the family in fostering the community integration of persons with TBI has gained more recognition. As the most basic unit of society, the individual's family has the potential to aid or impede recovery from TBI. Persons with TBI are frequently dependent upon family members in a variety of areas, including transportation, finances, leisure, and emotional support (5). A healthy family environment is likely to contribute to better adjustment for the person with injury. Unfortunately, there is ample evidence that TBI results in substantial emotional distress for family members. Family members who are distressed are less likely to be able to provide the support that persons with TBI need as they transition from the rehabilitation setting into the community. In spite of the evidence for family distress after injury, there has been relatively little focus on family intervention as part of the rehabilitation process. With the decreasing length of rehabilitation

stays, the focus is often on training family members to care for the most immediate needs of the person with injury. There is minimal time to prepare family members for long-term cognitive and behavioral changes in the person with injury. There is even less time available to address the emotional needs of family members and to assist them in coping with the impact of injury on their life and relationships.

The purpose of the current chapter is to provide a framework for intervening with family members to assist them in managing injury-related stress and in helping the person with injury to compensate for difficulties in a way that will maximize participation. The chapter will begin with a brief review of the research on the impact of TBI on family members. A framework for conceptualizing the factors that contribute to family members' distress after injury will then be introduced. This framework will be used as a basis for proposing components of a family intervention program. Next, a theory-driven and comprehensive intervention program for family members will be introduced. The chapter will close with recommendations for future directions in conducting interventions with family members. The information in this chapter will be applicable to family members of persons with moderate to severe injury. There has been minimal research on the impact of mild TBI on the family.

## WHAT IS THE IMPACT OF TBI ON THE FAMILY?

The research conducted over the past 30 years has been unequivocal in showing the emotional impact of TBI on family members (6–9). Family members report clinically significant amounts of depression and/or anxiety at the period between 3 months and 1 year post-injury (10–14). They also report significant levels of stress or “perceived burden” related to symptoms in the person with injury (13–17). While most persons with TBI show some improvement in symptoms over time, the research has shown that family distress actually persists and in certain cases increases over time. Substantial emotional distress has been noted in family members as long as 5 and 7 years after injury (12, 16–18). The persistence of distress is likely related to the type of symptoms that tend to endure in the person with injury. While substantial improvements are usually noted in physical, cognitive, and emotional symptoms over the first year after injury, some type of impairment often remains (19). The most enduring symptoms tend to be changes in emotions, social interaction, and higher level cognitive skills (e.g., organization, self-monitoring) (19). Changes in emotional functioning and social interaction skills have been shown to contribute most to family members’ distress (20–23). Evidence of family members’ emotional distress is manifested in the fact that they seek services for mental health problems more frequently after injury and they make greater use of alcohol and other drugs (24). There is evidence that a large proportion of family members have backgrounds that could predispose them toward having adjustment difficulties following injury. These backgrounds include pre-existing emotional difficulties and unhealthy family interactions (25).

Family members’ emotional distress may be partially related to other types of changes that they experience after injury. Relationships among family members often change in a negative way after injury (12, 26, 27). The person with injury is often unable to resume the roles formerly held within the family. Some of the roles vacated by the person with injury may be action roles, such as earning money or performing chores, and others may be emotional, such as being the person who people turn to in times of trouble. The roles that the person with injury can no longer fill are usually taken over by another family member. The result is often that certain family members are attempting to fill too many roles, resulting in role strain. Role strain can have a negative impact on physical and mental health. Another type of change in relationships resulting from TBI is decreased communication among family members (12). Due to the increased time demands related to caring for the person with injury and taking over unfulfilled roles, there is typically less time for quality family interaction. Impaired communication,

particularly with regard to social skills and pragmatics, is common in persons with TBI and may impact the ability of family members to interact with one another. In certain cases, the person with TBI may have difficulty controlling verbally and/or physically aggressive behaviors, affecting the quality of family relationships.

Injury-related stress and changes in the person with injury may have a negative impact upon sharing of warmth and affection among family members (12). Especially for marital partners, injury often results in decreased intimacy and satisfaction with the relationship (26–28). Decreased intimacy can result from a combination of cognitive and behavioral changes in the person with injury, the emotional reaction of spouses or intimate partners to the injury, and environmental stressors, such as decreased finances and decreased time to devote to relationships. Spouses have reported that serving in the caregiving role for a person with TBI places them in a parent-like relationship that is incompatible with their role as an intimate partner (29). Partners often find changes in the person with TBI, such as dependent behaviors and disinhibited sexual comments, unattractive (30). Intimacy is further decreased by the fact that 1/3 to 1/2 of persons with TBI experience some form of sexual disturbance, including decreased drive and/or arousal, impaired physiological response, and decreased ability to achieve orgasm (31–34).

Another type of difficulty that family members often face after TBI is social isolation (6, 35). Immediately following the injury, family members typically experience an increase in social support. Friends, neighbors, church associates, and extended family typically rally during a catastrophic event such as a life-threatening injury. This immediate increase in support often wanes with time. Recovery from TBI is a long process, and for some persons, impairments endure for a lifetime. Sustaining social support for this length of time is rare for most family members. As time goes on, persons who initially provided support often visit and call less frequently. This decline in social support over time is a phenomenon that is typical following most catastrophic events. However, it may be compounded in the case of TBI due to emotional and behavioral deficits in the person with injury. Changes in social interaction skills are difficult for persons unfamiliar with the effects of TBI to understand. People who could provide support for family members may feel awkward interacting with the person who is injured, and may react by avoiding interactions with them and their family. In other cases, family members of persons with injury may withdraw from others because they are embarrassed by the social behaviors of the person with injury (6). In either case, the result is usually that the person with injury, as well as their family members, become isolated. This isolation usually occurs at longer post-injury intervals, when rehabilitation and other medical services have ended, further increasing isolation.

## WHAT PREDICTS FAMILY MEMBERS' RESPONSE TO TBI?

Understanding what enables some family members to adjust relatively well to injury-related changes while others deteriorate physically or mentally is an important first step toward developing appropriate interventions. One possibility is that the family members of persons with more severe injuries and greater impairments will experience greater distress. However, this hypothesis has been only partially supported. While injury severity has been shown to be related to caregivers' distress at 3 to 6 months post-injury, little relationship has been found at longer follow-up periods (10, 11, 15, 21–23, 36). Regarding impairments in the person with injury, changes in emotional functioning and social interaction changes have been found to be related to caregivers' distress (14, 18, 20–23, 37). The relationship between caregivers' distress and cognitive deficits in the person with injury has generally been moderate (15, 22, 23). Physical impairments in the person with injury have not been found to contribute much to caregivers' distress (15, 22, 23).

There is some evidence that spouses of persons with TBI experience greater stress than do parents (22, 23). There are a couple of possible reasons for this. First, parents who care for adult children with TBI are returning to a caregiver role that is familiar to them. While they may not have been in that role with their child for many years, the familiarity of the role may reduce stress somewhat. In contrast, a husband or wife caring for an injured spouse is forced into a role that is likely unfamiliar and uncomfortable. Many family members describe the behavior of the person with injury as being more childlike. It is possible that parents may have an easier time accepting childlike behavior in their adult child than will a spouse. A second possible reason for decreased stress in parents relative to spouses may be that many parents will have a spouse or partner to assist them in the caregiving role. In contrast, a husband or wife caring for an injured spouse does not have the instrumental or emotional support of a partner. In addition, their relationship may have changed in a way that has them grieving for the loss of a significant partnership. It is important to realize that the research has not been conclusive in showing that parents experience less stress than spouses (10, 11, 21, 38). Many parents caring for an injured adult child may experience substantial stress on having their child return to a dependent role at a time in life when they were looking forward to retiring and relaxing. The switch in role may also lead to the emergence of dependence and autonomy struggles that had been earlier resolved during the child's transition to adulthood. Reemergence of these struggles can be very stressful for all involved.

There has also been some evidence that male family members experience greater stress in the caregiver role

compared to females (39, 40). This finding may be partly due to the fact that the caregiving role may be more familiar for many females. Males may also be overwhelmed by the variety of roles they have to assume if their wife is injured. In many households, the wife typically bears the primary responsibility for childcare, household chores, and planning social activities. When the wife is injured, her husband is faced with taking over these roles, as well as maintaining employment. For many men, this results in substantial role strain. Finally, males may be less likely to seek emotional support or to share their emotions with others, making it more difficult for them to cope with stress.

The research to date has shown that injury-related characteristics and demographics only partially explain family members' response to TBI. Professionals who work with families after TBI realize that individual characteristics unique to different family members impact the way that they cope with the injury and related changes. Characteristics unique to individuals, such as coping style, cognitive appraisals of the caregiving situation, and social support can impact their response to stressful situations (41, 42). Coping skills, cognitive appraisals, and social support serve as a buffer between stressful events and family members' physical and mental health. This model has recently been adapted for caregivers of persons with TBI (40, 43). Due to its applicability to designing family interventions, the model and supporting evidence for caregivers of persons with TBI will be discussed in detail below.

## A GUIDING MODEL FOR UNDERSTANDING FAMILY RESPONSE TO TBI

The model below has been adapted from previous research on stress and coping theory in individuals and in families (41, 42).

The model proposes that the relationship between the injury and family members' response, as operationalized by their physical and mental health, is not a direct one. Response to the injury is mediated by family members' coping styles, their perception or appraisal of the caregiving role, and the social support they have available. The model explains why 2 different family members who are caring for persons of similar injury severity with similar types of impairments can have different responses. Each individual is unique with regard to coping skills, the way they view events, and their social networks.

In the past 5 years, several studies have investigated the relationship of various components of this model to caregiver distress. Several studies have found that the coping style of caregivers is related to their distress (37, 40, 44, 45) Specifically, the use of strategies such as escape-avoidance (e.g., wishing that the problem would go away)



and accepting responsibility or blaming oneself is related to higher levels of emotional distress in caregivers (46). Use of spiritual support, use of social support, and reframing of negative thoughts have been found to be associated with less stress and burden (45). The amount of social support that caregivers have available has also been shown to be related to distress (44, 47). However, one study indicated that it is caregivers' satisfaction with social support rather than the actual amount of support that predicts distress (40). The contribution of cognitive appraisals to caregiver distress has not received as much attention as the other components of the model. Struchen and colleagues (48) adapted a measure of caregiver appraisal, The Caregiver Appraisal Scale (49), that had been developed for use with caregivers of persons with dementia. They showed that the scale had validity for use with caregivers of persons with TBI and that negative appraisals were related to greater emotional distress. The subjective burden measure used by Brooks, McKinlay, and colleagues (15-17) can be conceptualized as an appraisal of the impact of injury, since it requires caregivers to rate the overall stress resulting from the injury. Sander and colleagues (40) found that scores on the subjective burden scale were significantly related to symptoms of emotional distress on a psychiatric inventory. They also provided evidence for the utility of the model shown in Figure 60-1. Level of impairment in the person

with injury (stressful event), coping strategies, subjective burden, and social support accounted for more than half of the variance in emotional distress.

### Implications of Research for Family Interventions

The research to date has shown that impairments in the person with injury contribute to family members' distress, and that impairments in emotional functioning and social behavior are most stressful for family members. However, family members' distress is also determined by characteristics unique to family members, including the coping strategies they use, how they perceive the injury and its consequences, and the social support they have and make use of. This information has implications regarding areas to target for intervention. Interventions may also be guided by the research on family needs conducted by Kreutzer and colleagues at the Medical College of Virginia. In a series of studies using their Family Needs Questionnaire, they documented that the needs rated as most important by family members were the needs to receive medical information (50, 51). Family members reported that they wished to receive information on the physical, cognitive, and emotional/behavioral changes in the person with injury. They also reported that they wished to have information presented in a clear and honest

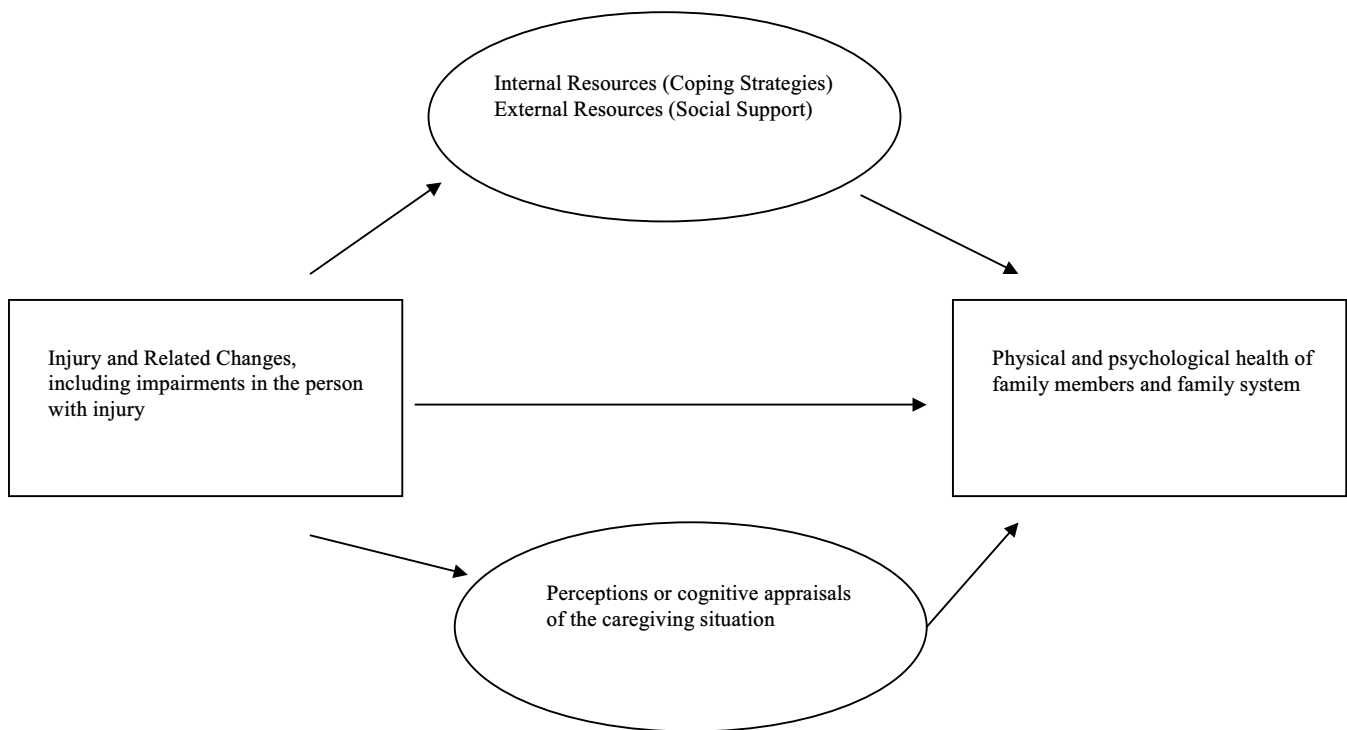


FIGURE 60-1

Model of family adaptation to TBI

manner. As part of these studies, family members were also asked to rate the extent to which various needs had been met. Family members routinely reported the majority of needs for medical information as being met. In contrast, they reported needs for emotional support and instrumental support (e.g., help with practical things like house-keeping) as primarily unmet. These needs were reported as unmet by most family members at long-term periods ranging up to 2 years post-injury (52). Unmet needs have been shown to be related to burden/stress for both African American and White caregiver of persons with TBI (53).

With funding from the National Institute on Disability and Rehabilitation Research, investigators at Baylor College of Medicine and The Institute for Rehabilitation and Research (TIRR) have developed an intervention for family members of persons with TBI. Guided by the research, they have proposed several crucial components of a family intervention program. The components are shown in Table 60-1.

The components shown in Table 60-1 address all of the areas that have emerged as important based on existing research, including provision of information, a focus on strengthening family relationships, improving coping skills, building support networks, and changing cognitive appraisals. These are all components that are proposed as important contributors to caregiver health, as shown in Figure 60-1. The interventions that have typically been offered in the acute and post-acute rehabilitation settings are usually focused on one only or two of these components. For example, education regarding the injury and its consequences, and how to manage cognitive and behavioral problems are a typical focus of many programs. Family members are usually referred to support groups in an attempt to meet their emotional needs. There is generally a lack of use of theory and research to guide interventions, with the result that there is not an integrated

program of intervention for family members that addresses all of the areas shown in Figure 60-1 to be important for family members' adjustment.

At Baylor College of Medicine and TIRR, investigators have developed an intervention program for family members that addresses each of the components shown in Table 60-1. An educational manual has been developed that provides information in all of these areas (54). The intervention has been carried out as a group treatment and as an individual treatment. The remainder of this chapter will be devoted to detailing this treatment and discussing caveats encountered when implementing the interventions.

### A Cognitive-Behavioral Intervention for Family Members

As mentioned above, the treatment has been conducted in both group and individual settings. The research regarding the use of the treatment in individual settings is still ongoing. It is believed that the group approach to family intervention will be the most convenient and economical in acute and post-acute rehabilitation settings. For this reason, the discussion below will describe implementation of the intervention in the group setting.

The group intervention takes place across 6 sessions, occurring weekly for 2 hours each. The intervention is a combination of psychoeducational and cognitive-behavioral treatment approaches. The group is led by a Master's level therapist, such as a Licensed Social Worker or a Licensed Professional Counselor. Each session combines didactic training with group therapy. Thus, participants benefit from the instruction of a professional experienced in TBI, but also benefit from sharing their experiences with other family members and forming a social network that can endure beyond the group. The contents of each group session are described below.

**TABLE 60-1**  
*Components of a Family Intervention Program*

- General education regarding TBI and its consequences
- Direct training in management of physical, cognitive, and emotional/social impairments
- Discussion of changes in family relationships and strategies to improve communication and positive interactions within the family
- Training in stress management techniques for family members
  - Education regarding negative impact of stress
  - Teaching of a relaxation technique
  - Training in effective problem-solving
  - Training in positive reframing of negative thoughts
- Education regarding local and national community resources, including support groups

*Session 1 (Introduction)* Session 1 begins with a general introduction to the group. The therapist explains that the group is being conducted because TBI affects the entire family. Emphasis is placed on normalizing family members' experiences. The therapist commends family members for their efforts to cope with the injury, and provides examples from clinical experience and from the literature regarding difficulties that other family members have faced. Emphasis is placed on the importance of family members attending to their own needs in order to be able to provide adequate care for the person with injury. The importance of emphasizing this point derives from the findings of Kreutzer and colleagues that family members typically place more importance on information regarding the person with injury and less importance on their own emotional needs. Family members often feel selfish if they focus on their own needs when their loved one with

injury requires attention. Family members may feel less guilty about attending to their own needs if they are convinced that doing so will also have a positive impact on the person with injury. Following the general introduction by the therapist, each participant introduces him or herself and tells their story regarding the injury and the events that have led them to the group. The sharing of these stories is an important part of the group experience that allows participants to form a bond that will enable them to be comfortable sharing information in future sessions. Following the sharing of stories, the therapist presents a metaphor that will be used throughout the remainder of the sessions. The metaphor is borrowed from Marilyn Colter Maxwell's book *Missing Pieces: A Coping Guide for the Families of Head Injury Victims* (55). Ms. Maxwell is the wife of a man with a brain injury, and she stated that "Living with head injury is like trying to work a jigsaw puzzle without all the pieces." Group participants are asked if they have felt this way at any time since the injury, and they are asked to share their experiences. The therapist makes notes regarding experiences of individual family members that can be used to personalize concepts taught during later sessions. The first session ends with an overview of the next 5 sessions. All participants are provided an educational manual to take home.

*Session 2 (General Education and Management of Specific Problems)* The second session contains the largest didactic portion of the intervention. The session begins with education regarding different types of TBI (closed versus penetrating) and the mechanisms of injury in each. The metaphor of jello floating in a container is used to illustrate what happens to the brain during injury. A neuroanatomically correct model of the brain is used to demonstrate the most common points of injury (frontal and temporal) and to describe coup-contrecoup lesions and the impact of diffuse axonal injury. Family members responded well to this portion of the intervention. For most participants, this was the first time the injury had been explained in such detail. Following the discussion of the cerebral changes resulting from injury, the therapist describes the most common changes occurring in the physical, cognitive, and emotional areas. Emphasis is placed on the fact that all human brains share many similarities, but each also has unique differences. Thus, participants are made aware that their family members' difficulties may share much in common with those of others, but may also be unique. The therapist discusses the typical pattern of improvement after TBI. Participants are told that the most rapid improvements occur within the first 6 months, with slower improvements occurring between 6 months and 1 year. They are informed that spontaneous improvement typically peaks between 1 and 2 years. However, they are provided with hope that daily functioning and quality of life can improve beyond 2 years

based on the implementation of compensatory strategies and environmental modifications to increase support. This is used as a segue to begin discussing strategies for specific problems in the person with injury. Participants are asked to complete a checklist of neurobehavioral symptoms observed in the person with injury. A checklist was developed as part of the educational manual, but any of the existing neurobehavioral inventories may be used. Once family members have completed the checklist, they are asked to pick 2 problems that result in the most stress for them and their families. The second half of the session is devoted to teaching family members specific strategies to assist the person with injury to compensate for deficits. The educational manual that was provided to family members during the first session contains strategies for all typical problems, so participants have access to help for difficulties that are not discussed during the session.

The strategies taught by the therapist are tailored to be specific to the needs of the participants and their particular family situation. For example, one of the problems that was particularly stressful for the wife of man with TBI was that her husband could not remember what to make for dinner. Her husband had been in charge of cooking dinner prior to injury, and apparently the family had very particular tastes with regard to meal plans. They were partial to certain combinations of food. For example, pork chops were always accompanied by applesauce, corn, and rice. Following the injury, this man no longer had accurate recall of the menu combinations, which was upsetting to his wife and daughter. Since flexibility in the meal plan was not an option that they would consider, the therapist suggested posting a weekly menu containing all the meal plans in the kitchen. The husband and wife wrote the menu together, and he successfully used it to independently prepare meals without having to call and interrupt his wife at work. Rather than attempting to change the dynamics of family interactions with regard to flexibility, which would require a family systems approach and more intensive therapy, the therapist was able to train this man's wife to compensate for the problem in a way that was satisfying to all involved.

The intervention has also shown success in teaching simple behavior management strategies to family members in the group setting. For example, the mother of a 20 year-old man with TBI experienced stress due to her son's perseveration on asking for money. He received a \$50 allowance once per week, but would repeatedly ask for money in between allotments. He would phone his mother often while she was at work, and would begin asking for money as soon as she got home. The mother was exasperated by this behavior, but felt helpless to change it. The therapist presented a simple behavior management plan to her. The first time that her son asked for money after his allowance was given, he would be reminded

that he was given money on Friday and would not be receiving more until the following Friday. He would be informed that the next time he asked for money, \$5 would be deducted from the following week's allowance. Five dollars would subsequently be deducted each time he requested money. The therapist cautioned the mother that this behavior could result in an increase in requests at first, but encouraged her to remain firm in carrying out the plan. This young man stopped requesting extra money within one week, resulting in less stress on his mother and an improvement in their interactions.

The two examples discussed in the paragraphs above are typical of the types of difficulties reported as stressful by family members. While neither of these examples represented life-threatening changes, they resulted in significant daily hassles and stress for the family members. When family members experience a catastrophic event such as TBI, their resources to cope with daily hassles is restricted. Helping them to gain a sense of control by attacking small problems can instill feelings of self-efficacy that can allow them to tackle larger problems. Within the confines of a group therapy situation, it is important for therapists to acknowledge their limits. It will be difficult to change family dynamics or solve large problems. Therapists should be aware of when to refer group participants for individual or family therapy. For example, attempting to alter severely aggressive behavior in the person with injury via group therapy with family members would not be recommended. Altering this behavior would require the therapist to have a detailed understanding of the environmental antecedents of the behavior and contingencies supporting the behavior. The time required to change this behavior is greater than that which could be given during the group session. The danger of escalating aggressiveness during the initial stages of a behavior management plan is an issue that should be closely monitored and is beyond the scope of the group setting. On the other hand, the group setting has been effective for teaching simple behavior management to reduce mild to moderate cussing behavior.

Therapists should always caution family members that each strategy does not work for everyone. Successfully implementing a strategy often requires practice and persistence, and initial failures are common. Family members are encouraged to phone the therapist between sessions to discuss difficulties implementing strategies in the home. The first minutes of the remaining 4 group sessions are devoted to discussion of participants' experiences implementing the strategies. This allows other group members to benefit from hearing the experiences of others and the therapist's suggestions for remediating difficulties. Other family members in the group often offer their own suggestions for strategies that may work. Participants are encouraged to abandon strategies that do not seem to work after repeated attempts. They are

referred to their educational manual for other strategies to try.

*Session 3 (Relationships)* The goal of this session is not to alter family dynamics or to impact the overall family system. Individual family therapy sessions would be required to accomplish that goal. Rather, the goals of the session are to help family members accept that changes in relationships are a natural occurrence after TBI, to help them become aware of changes in their own family and process their feelings regarding these changes, and to help them develop ways to improve communication within their families and increase the quality of time spent together. The session begins with the therapist discussing some changes that family members have typically noted after TBI, including changes in roles, decreased communication, and less quality time together as a family. The therapist begins discussing common role changes within the family, including action roles (e.g., breadwinner, cooking, financial management) and emotional roles (e.g., the "rock" whom everyone turns to in times of trouble; the "clown" that makes everyone laugh in hard times). The therapist discusses the likelihood of role strain after injury and the negative impact that this can have on physical and mental health. Family members are encouraged to complete a chart stating the roles of different family members before and after injury. They are invited to share their stories about role changes in their families. The therapist assists them in finding ways that roles can be renegotiated to reduce strain on family members. Following the discussion of role changes, the therapist initiates discussion of changes in communication and positive interactions within the family. Changes in communication and interactions are explained as resulting from a combination of changes in roles and schedules, as well as the overwhelming nature of the injury and the prominence it has gained in dictating daily life. Participants are encouraged to share their stories regarding changes in communication and interaction within their families. The therapist assists them in developing ways to improve communication and time spent together. For example, family members are encouraged to spend some time together viewing old photos and reminiscing about happier times. Such activities reinforce their unity and emphasize the positive aspects of their relationships.

The topic of sexuality is addressed in an educational way within this session. The therapist mentions that many persons with TBI experience a disturbance in sexuality and explains some of the most common forms of sexual dysfunction. The therapist also explains how the self-esteem of persons with injury can be affected, and how this can impact their sexuality. Finally, the therapist normalizes the feeling that some partners may feel less attracted to a person with TBI.

The session on relationships is the least structured of all the sessions. Therapists should be sensitive to the

level at which various participants have processed changes within their family relationships. Participants should not be pushed to acknowledge changes that they are not ready to process. Some family members may be using denial as a way to cope with negative relationship changes. Therapists should not attempt to break through this denial within the group setting. Sexuality is often a difficult subject for family members to discuss. Therapists should provide an atmosphere open to discussion of these topics by family members who are ready, but should not push them to disclose personal information. The goal is to normalize relationship changes within the context of TBI and to set the stage for later change if family members feel the need. The therapist emphasizes the positive impact of family therapy, including sexual therapy, for some families, and informs participants that they can request a referral at any time.

*Session 4 (Stress Management I: Education, Relaxation, and Coping)* The goals of this session are to educate family members in the negative impact of stress on the mind and body, to train them to use a simple breathing exercise to relax, and to teach them to identify their coping strategies and evaluate their effectiveness. The therapist begins with a visualization exercise. Participants are asked to close their eyes and imagine themselves walking through a forest on a beautiful spring day. Various sensory aspects of the scene are described, and participants are encouraged to imagine themselves feeling completely relaxed. They are then instructed to visualize a snake, coiled and hissing, on the path in front of them. The therapist then leads them through a discussion of the physical changes they notice in their bodies (e.g., sweating, rapid heartbeat, rapid shallow breathing). This segues into a discussion of the adrenaline response and the negative impact of stress on the mind and body. Participants complete a stress symptom checklist to help them become aware of signs that can warn them of stress. Each participant shares their pattern of stress symptoms with the group.

The therapist then introduces a simple breathing exercise. This exercise was adapted from the workbook *Managing Stress Before It Manages You*, by Caudill (56). The exercise involves participants lying down on mats or sitting in a position that is comfortable for them. They are instructed to close their eyes and imagine a balloon in their abdomen. They are told to breathe in deeply and slowly and to imagine the balloon filling with air. They are then told to exhale slowly and fully, imagining the air seeping out of the balloon. The therapist encourages them to imagine the stress leaving their bodies like the air leaving the balloon. Participants complete a visual analogue scale to rate the amount of stress they are experiencing immediately prior to and immediately following the breathing exercise. They are encouraged to practice the exercise at least twice per day for the next week and to

rate their stress before and after each practice. In order to increase the possibility of them practicing the techniques, the therapist asks them to schedule specific times of day to perform relaxation exercises. The therapist emphasizes that learning to relax takes practice and encourages them not to give up if it doesn't seem to be working right away. They are also informed that not every relaxation exercise will work for everyone. They are referred to their educational manuals for other relaxation exercises that may work for them. The manual includes details about how to carry out progressive relaxation and visual imagery exercises. The breathing exercise was chosen over these others for implementation in the group because it is simple, brief, and can be used easily by family members in a variety of settings, even outside of the home.

The second half of session 4 focuses on the development of effective coping strategies. The therapist begins by pointing out that family members are all coping the best way that they know how. However, TBI is different from anything that they have experienced before, and not all of the coping strategies that they've used in other situations may work well in their new situation. The therapist presents several coping strategies that other family members have reported as helpful, as determined by Willer and colleagues (57). These strategies include taking time out for yourself, maintaining a sense of humor, being more assertive, trying to see things more realistically, being careful not to blame everything on the injury, and renegotiating roles and responsibilities. Group members are asked to discuss whether they've found any of these strategies to be helpful in coping with the results of TBI and are encouraged to provide additional strategies that they have found beneficial. The therapist next emphasizes the importance of evaluating coping strategies to make sure they are helpful. Participants are provided with a chart to use when evaluating coping strategies. The chart is shown in Appendix A. The goal of evaluation is for family members to learn to question whether the things they do to cope are leading to the results they desire. They are encouraged to think of alternative coping strategies for those that do not lead to the desired result. The therapist encourages family members to use the chart to evaluate strategies that they use to cope with stressful situations over the next week.

*Session 5 (Stress Management II: Problem-Solving and Overcoming Negative Thinking)* The goals of session 5 are to train family members in a systematic approach to solving problems and to teach them to reframe negative thoughts into more positive, self-empowering thinking. The session begins with the therapist defining a problem as anything that requires a solution or decision. Thus, problems can be very small (e.g., deciding what to have

**TABLE 60-2**  
**Steps Toward Effective Problem-Solving**

Identify the problem
Brainstorm solutions
Evaluate the alternatives
Choose a solution
Try the solution out
If the 1st solution doesn't work, try another one and repeat the evaluation procedure

for dinner) or very large (e.g., deciding which bill to pay when you only have the money to pay one). The therapist emphasizes that the injury has likely resulted in family members having to make so many decisions that they become overwhelmed. The therapist explains that when people feel overwhelmed, even making small decisions can become difficult. Participants are informed that the purpose of learning a systematic way to approach and solve problems is to help narrow down alternatives so that decision-making is easier. They are encouraged that effectively solving problems will lead to reduced stress and an increased confidence in their ability to solve larger problems. The therapist then introduces the problem-solving steps shown in Table 60-2.

When identifying the problem, participants are taught to break complex problems down into smaller steps in order to make it more manageable and to increase the probability of success. They are encouraged to choose the easiest problem first in order to build confidence for more difficult problems. Participants are taught to brainstorm all possible solutions to the problem, even ones that may appear unrealistic at first glance. They are then taught to generate pros and cons for each possible solution, and choose the solution that should lead to the best outcome. The therapist explains that the best solution is not always the one with the highest number of pros and the lowest number of cons. Some pros or cons carry more relative weight than others. When a solution does not seem to work, participants are encouraged to attempt to determine why. At times, this will lead to a new problem that requires a solution. At other time, it will lead to abandonment of the solution and the trying out of new solutions. The therapist emphasizes persistence in repeating the problem-solving steps until a satisfactory solution is achieved. A particular problem that was raised by a group participant during a previous session is then used by the therapist to illustrate working through the problem-solving steps. Family members are encouraged to practice the steps on a real-life problem during the following week.

The second half of session 5 focuses on training in overcoming negative thoughts. The session begins with a simple exercise aimed at helping group members

become aware of the impact that thoughts can have on feelings and behaviors. The exercise follows:

*Your friend says to you, "I found a great new hairstylist and I'll give you the number." How would you feel if you thought that your friend was implying that your hair is looking terrible, and you need some help? [Have them discuss how they would feel and how they might act toward the friend.] Now think about how you would feel if you thought that your friend was really excited about finding a great hairstylist and simply wanted to share it with people she cares about. [Have them discuss how they would feel and how they might act toward the friend.] In this situation, you would feel and act differently depending on the way you thought about what was being said.*

The therapist next explains the ABC model of the relationship between thoughts, feelings, and actions (58). The model specifies that an event or situation (A) does not directly impact feelings and actions (C). The event results in certain thoughts (B) that in turn impact feelings and actions. The therapist emphasizes that while family members may not be able to change the injury or its consequences, they do have power to change the way that they think about things. Participants are provided with a handout containing "The Ten Forms of Twisted Thinking", from David Burns' *Feeling Good Handbook*. (59) This handout describes common forms of irrational thinking that are considered counter-productive to combating stress. For example, overgeneralization is an irrational thought that occurs when someone views a single bad event as indicative of all past and future events. An example is thinking, "My husband's disability claim was denied the first time we tried. I guess we'll never be able to get any financial help." Group members are provided a chart with which to evaluate their thoughts in different situations. The chart is shown in Appendix B, along with an example. Family members are taught to reframe negative thoughts into positive thoughts that instill hope and self-confidence. As shown in Appendix B, the positive alternative thought for denial of the disability claim would be that many people are denied the first time and that better documentation of deficits may result in approval of the claim. Family members are encouraged to use the chart to evaluate their thoughts in different stressful situations over the next week. During the session, the therapist helps group members to identify one negative thought that they have often and to develop a positive alternative thought. They are provided with index cards, with the phrase "DON'T THINK \_\_\_\_\_; THINK \_\_\_\_\_." For example, a card may read "DON'T think we'll never get financial help; THINK we will gather more information in support of our claim and try again." These cards can be placed on their refrigerator, on their desk at work, or anywhere else they find convenient. The

card will serve as a reminder to them to replace negative thoughts with positive ones.

*Session 6 (Accessing Local and National Resources and Wrap-Up)* The last session begins with the therapist reviewing the most common local and national resources family members can turn to for help. The therapist next reviews the highlights of the 6-week group in order to reinforce the material learned. Group members are encouraged to discuss their thoughts about the group, including which parts they found to be beneficial and what they were sorry to not see included. Participants are referred to local support groups in order to continue social support. Family members have also benefited from encouragement to become involved in state Brain Injury Associations and/or in local advocacy groups. The final session is also used to complete satisfaction surveys and any evaluative measures. Areas typically assessed include emotional distress, caregiver appraisals, coping skills, and social support before and after completion of the group.

### **Initial Experiences with the Group Intervention**

As part of a NIDRR-funded project, the group intervention was piloted at 3 centers: The Institute for Rehabilitation and Research (TIRR) in Houston, Methodist Rehabilitation Center in Jackson, Mississippi, and The Mayo Clinic in Rochester, Minnesota. The groups were conducted with family members of persons who had sustained TBI 1 to 2 years prior. In all cases, the persons with injury had received comprehensive inpatient rehabilitation at the participating center. However, family members and the person with injury were not receiving any rehabilitative services at the time of their participation in the group. Two separate groups were conducted in Mississippi and Minnesota, and one was conducted in Houston. There were 3 to 4 participants in each of the groups. All group participants reported satisfaction with the contents of the group. In all cases, they reported that they learned information in the group that they had not heard previously regarding the injury and its consequences. While all family members had been participants in the inpatient rehabilitation process, they had obviously either not been exposed to this detailed information or had not been ready to process it at the time they had heard it. Some specific comments made by group members on the satisfaction survey were that they had learned not to feel guilty about wanting to take time for themselves and that they had learned that the behavior of the person with injury was due directly to brain injury and not to purposeful behavior. Family members also verbalized satisfaction with the social networking afforded by group participation. Some family members exchanged contact information in order to keep in touch after the group disbanded. At one center, one of the groups made plans to

continue meeting after the therapist-led group was completed. While the intervention has shown success in small pilot groups, its effectiveness should be tested in clinical trials. Plans are currently underway to conduct this research.

### **Future Directions for Interventions with Family Members**

*Home-Based Therapies* One of the reasons that the treatment groups described above were so small was that it was difficult to find a common time that was convenient for several family members to meet. The daily lives of families are particularly hectic in the months following TBI. Persons with injury and their family members often have difficulty attending facility-based treatments, even when they report on needs surveys that they desire services. This may be especially true for persons from low educational and/or socioeconomic backgrounds. Persons from these backgrounds often have difficulty obtaining transportation to appointments. In addition, they may feel less comfortable in a research facility or rehabilitation facility. On surveys conducted at TIRR, persons have often reported that they feel more comfortable receiving treatments in their own home or communities. Conducting treatments in the settings where people carry out their daily activities has been proposed as an important alternative to facility-based treatments (60). Conducting family interventions in the home has several advantages. First, it is convenient and economical for most family members. Second, it allows therapists to observe families and the person with injury within the home environment, where they can view problems as they occur. This allows therapists to suggest compensatory strategies that are truly tailored to the environment in which activities will be carried out. Third, facility-based interventions often result in uncertain generalizability to the home and community. Conducting therapy in the home has the potential to improve generalizability. Finally, intervening in the home environment often improves the rapport between the therapist and client. Trust and acceptance are more likely when the client sees the therapist as willing to enter their world and attempt to understand them in their own environment. A study is currently being conducted at TIRR to evaluate a family intervention conducted in the home setting. The family members are from primarily low education and low socioeconomic backgrounds. The rate of therapy completion using home-based treatments has been superior to that obtained when conducting facility-based treatments. Therapy members have generally welcomed research staff into their homes and the information gained through observation in the home setting has been invaluable. Given these advantages, it is recommended that family intervention be conducted in the home setting when possible.

*Culturally Sensitive Interventions* TBI is not a disorder that occurs equally among persons of different backgrounds. TBI is disproportionately represented among minorities and among persons of low socioeconomic status (SES) (61, 62). In spite of this, most persons from minority and low SES backgrounds do not have access to rehabilitation services. Family members in these groups are left to care for persons with injury at an early stage in the recovery process, with minimal training or assistance. Targeting interventions at this population of family members is very important. However, conducting therapy with these family members is often a challenge. They typically read below the 7th grade level, which renders many existing educational materials unhelpful. They often have difficulty relating to the language used by most therapists. For example, they may have difficulty describing their “feelings” about events and may focus more on concrete changes. They also may have difficulty trusting medical professionals due to previous difficulties and disappointments.

Family members from different racial/ethnic groups may hold beliefs that put them at odds with the practices of rehabilitation professionals. For example, many Hispanic persons place primary importance on physiological recovery and do not have a conceptual framework with which to discuss cognitive and emotional issues (63). Professionals should take extra time when providing education to these family members and should avoid using psychological terms. Hispanic persons also tend to subjugate their individual needs to the needs of the family (63). This belief may make it difficult for family members to express negative emotions regarding the injury and any negative feelings they may have toward the person with injury. Normalization of negative emotions will be especially important for these families. Another commonly held belief among Hispanic persons is that external agents (e.g., God) have a greater role in determining their future than they themselves do (63). This belief may result in difficulty understanding the importance of making changes in the environment of the person with injury and developing compensatory strategies. Consulting with experts in the areas of cultural sensitivity will be important for establishing rapport with these groups and for developing interventions that can serve the needs of these populations.

It is also possible that persons from different backgrounds have different priorities in terms of family needs. For example, many minority family members have extended family and support networks, which may result in less distress compared to Caucasian family members. Future development of family interventions that are tailored to the needs of diverse groups of people would be beneficial. Educational materials should be written at a 7th grade level or below. The use of the World-Wide web to disseminate materials to family members is likely to

result in a cultural gap in access to information. In a recent survey conducted within the Houston Harris County Hospital District, family members from a low education and low socioeconomic background expressed a preference for receiving videotaped compared to written educational materials. Translation of materials into languages other than English is crucial for equal access. Finally, extensive outreach will be important in reaching persons from low education and/or low SES backgrounds. Family members in these groups often do not seek help within medical facilities, and they often fall between the cracks of traditional rehabilitation services. Reaching these family members will require actively reaching out within community settings, such as health care clinics and churches.

*Timing of Interventions* The group treatments conducted at TIRR have included family members of persons who sustained their injuries one to two years ago. Studies currently underway are investigating home-based interventions with family members at approximately 6 months post-injury. Conducting interventions beyond the acute period is important based on the research showing that family members’ distress often increases with increasing time post-injury. This is thought to occur because during the initial 6 months after TBI, rapid improvements are usually noted. During this time, family members often hold out hope that things will return to normal. It is only when spontaneous recovery starts to peak and change becomes slower that family members begin to realize there may be permanent change. Unfortunately, this is also the time that rehabilitation services have usually been terminated and family members are caring for the person with injury on their own. Family members typically have many unanswered questions at this point. Providing education during the acute phases of recovery may not always prepare family members for long-term changes. Over the years, it has been noted that family members typically do not recall information that was provided to them early after injury. They tend to only process information that is applicable to the situation at the time. Furthermore, the shock and grief experienced by family members early in the recovery process may be an obstacle to learning information. Future interventions should be tailored to the phase of recovery that family members are experiencing. Recent studies have indicated that needs for information and involvement with care are predominant during the acute phases of recovery (64). Once persons are discharged and are living in the community, family members report needs for service delivery, advocacy/empowerment issues, and social support (65). The research supports that family members need intervention at all time points after injury, including in the long-term. Development of outreach services will be crucial for meeting these needs.



## APPENDIX A

*Evaluating Coping Strategies*

SITUATION	WHAT I DID TO COPE	WHAT HAPPENED	POSITIVE OR NEGATIVE?	OTHER STRATEGIES THAT MAY HAVE WORKED
We needed to see the Doctor because my family member ran out of medications, but there was a 2 month wait list.	Yelled at the receptionist and told her that was a ridiculous amount of time to wait.	Appointment time was not changed. My family member still didn't have his medicine.	Negative	
	Did nothing- just waited until the appointment.	Appointment time was not changed. My family member still didn't have his medicine.	Negative	
	Explained that he's out of medications and asked if he could get a temporary refill until the appointment.	Appointment was scheduled. Medication was refilled.	Positive	

## APPENDIX B

*Evaluation of Negative Thoughts*

UPSETTING OR STRESSFUL SITUATION	NEGATIVE THOUGHTS	WHY THIS ISN'T REALISTIC	POSITIVE, REALISTIC THOUGHT
Example: Your family member's application for Disability benefits was denied.	<p>"We will never be able to get any financial help."</p> <p>"They should have approved our application the first time."</p> <p>"No one cares about us."</p>	<p>One instance doesn't tell you how things will be in the future. People are just following the rules and may not understand the details of your situation.</p> <p>This situation has nothing to do with people's feelings for you or your family member.</p>	Lots of people are denied the first time. We will try again and explain our situation in more detail. If we don't get approved, we will look for other sources of assistance.

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# 61

## Return to Work Following TBI

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### INTRODUCTION

Vocational rehabilitation efforts in traumatic brain injury (TBI) have paralleled the increasing survival rate for those experiencing severe injury. Clearly, there have been more expanded efforts at ways of assessing and intervening vocational outcomes of persons with traumatic brain injury in the United States and worldwide. Work is increasingly viewed not only as an extremely worthwhile outcome economically, but therapeutically as an excellent means of enhancing cognitive and physical rehabilitation (1).

The natural course of work return as established by Dikmen et al. (2) suggests that 38 percent of adults with a severe injury, 66 percent of those with a moderate injury, and at least 80 percent of those with a mild TBI return to work within two years of injury. This particular study involved 366 consecutive admissions to a level 1 trauma center who considered their primary role activity to be working. Job retention, however, was not taken into consideration. Vocational rehabilitation intervention may or may not have occurred for this sample.

From the perspective of vocational rehabilitation research and demonstration projects with definite vocational intervention, most of these efforts are focused on adults experiencing a severe injury—Glasgow Coma Scale (GCS) score  $\leq 8$ , post-traumatic amnesia  $>7$  days, or duration of coma  $>24$  hr. A summary of these studies suggests work access in the range of 50–80 percent, with

retention dropping into a range of 50–65 percent of those placed (3) with a second placement considered “almost normative.” Wehman et al. (4) have suggested the use of a standard “monthly employment ratio” (percentage of months in which an individual worked half-time or more divided by months available for work) as a more standard manner of assessing employment success across projects. The reasons for variance in work return across studies, however, is a function of a range of study differences (e.g., lack of clear severity indicators, varying neuropsychological baseline measures, variance in time to rehabilitation and follow-up points, variance in defining outcome variables, etc.) (4).

There have been a wide and varied range of brain injury vocational rehabilitation research and demonstration efforts. Under private sector managed care, companies such as New Medico, Sunrise-Mediplex, Learning Centers, and others were unable (due to funding limitations) to sustain post-acute rehabilitation programs. As a result, a number of professionals who were focusing their energies in the TBI vocational rehabilitation field were forced to find other work endeavors. The Affirmative Industries (leased employee) work transition model, as described by Fraser et al. (5) at a Wisconsin New Medico program, was a benchmark program allowing *diverse, paid work evaluative experiences* for program participants in a residential program. This comprehensive program has not yet been replicated.

As has been noted, most of the existing vocational rehabilitation research has been focused on the moderate to severe injury cases. This is chiefly because most of the individuals involved in post-acute rehabilitation efforts, to include neuropsychologists and other rehabilitation staff, indicate that more than 80 percent of individuals with a mild traumatic brain injury or post-concussive syndrome concerns respond well to rehabilitation and have their issues resolved within a year of onset (6) or don't really need rehabilitation. Much of the concern here can really be the need for diagnostic specificity in mild TBI or post-concussive syndrome cases (e.g., a specific memory deficit, headaches, post-traumatic stress disorder concerns, etc.) and tailored intervention. In general, individuals with mild TBI are not referred to intensive vocational programs or relevant programs are simply not available.

In this chapter we will focus not only on specific return to work issues, but also those critical related factors such as health insurance, benefits planning, community supports, and career counseling in terms of work supports but community issues which affect employment. We begin with a review of the return to work (RTW) literature, with emphasis on those who experience more significant TBI.

### **Review of TBI Return to Work Literature**

Traumatic brain injury can result in variety cognitive deficits, impaired psychosocial functioning, and physical or sensory functioning (7). As a result, individuals with TBI often experience difficulty becoming competitively employed post-injury and maintaining employment for extended periods of time (8–12). Young male adults have the highest risk in sustaining TBI (13), and because the survival rates after injury have dramatically increased due to medical advancements, they are anticipated to have long life expectancies and it becomes imperative that they become employed after recovery. However, high post-injury unemployment rates are continuously being reported. Post-injury employment rates range from 10 percent to 70 percent depending on the study, while pre-injury employment rates range from 61 percent to 75 percent (14–17). It is suggested that this variance in post-injury employment rates is mainly caused by various measures used for injury severity, method of return-to-work process, inconsistency among employment status, and absence of long-term follow-up (3, 14).

Numerous studies have been conducted in an attempt to determine variables that influence individuals returning to work after sustaining TBI. The relationship between injury severity and regaining employment has been examined extensively, but the findings vary depending on the measure used (17). The relationship between returning to work and duration of posttraumatic amnesia

has not been identified (18, 19). Those who returned to work were likely to have shorter duration of coma and were in inpatient rehabilitation for a shorter period (2, 19). Those who returned to work obtained better scores on standardized instruments at admission such as Glasgow Coma Scale (20).

Age at injury was a significant predictor of returning to work for individuals over age 60 (21). Age between 40 and above at the time of injury negatively affected returning to work (2, 17–19, 22–24). The age of individuals returning to work or to school was younger than those who did not (16, 19).

Marital status has been found to have significant relationship with returning to work (16). Individuals classified as married had a lower rate of returning to work compared to those classified as single. There is contradictory evidence regarding gender. While Ip et al. (16) reported no significant difference between gender and returning to work, McMordie et al. (17) reported that females are more likely to regain employment than males, possibly due to females sustaining less severe injury than males.

Educational level and occupation pre-injury has also been examined. Low education level negatively influenced returning to work (16, 18). Persons whose previous employment was either semi- or unskilled manual jobs were reported to have less success in regaining employment (25) and individuals who worked in structural occupations such as building and trades were more likely to return to their former occupation compared to those who were professional, managerial, clerical, or service workers (15). This contradicts studies that indicate greater likelihood of individuals with more education and technical skills having success in returning to work (26). Among those who regain work after TBI, more individuals start a new job rather than going back to their previous one. However, those who were hired by their previous employer remained successfully employed and had higher hourly wages than those who were employed by a new employer post-injury (27).

The effect of race on regaining work after TBI has only recently begun to be examined and the results are contradictory. For example, Greenspan et al. (28) reported that race appeared to be related to failure to regain employment one year post-injury, whereas O'Connell (29) found race to be not significant. Rosenthal et al. (30) examined whether minority status affected short-term and one year functional outcomes and community integration for TBI patients. Regaining employment after TBI was found to have a significant relationship with both pre- and post-injury employment status. This may be due to the relatively low percentage of pre-injury employment rate among minority subjects, if the assumption is made that pre-injury employment provides the skills and attitudes that are needed in post-injury employment (31) and may also

be caused by differences in access to health care (32). Wright (33) summarizes that minorities with disabilities are less likely than whites to receive rehabilitative services, do not receive the same quality or quantity of services, and have poorer outcomes after rehabilitation.

A low level of social support is reported to have negative influence on returning to work (25, 34). Individuals with TBI receive a considerable amount of support while they are in post-acute care facility and also during return-to-work process from vocational rehabilitation personnel. However, after they are discharged and begin the return-to-work process, many require non-professional support, such as from families and community. This becomes an issue for persons sustaining TBI because many individuals with TBI are at a risk of becoming socially isolated (35).

Cognitive issues such as new learning and memory, impaired self-awareness, pre-existing and post-injury dysfunctional behaviors to impede return to work (4). However, not all impairments were identified as being barriers for persons with TBI to return to work or in maintaining employment. They became barriers if they affect achievement of their vocational goal and job maintenance for that particular individual (36). These included cognitive issues followed by emotional functioning, physical impairments such as hemiparesis, stamina or motor deficits, and characteristic and behavioral propensities that existed pre-injury.

Having a significant physical disability (37), psychosocial impairment (38), and cognitive impairment (39), history of alcohol abuse (16, 40) have been associated with impeding returning to work. Acquired deficits in the areas of social behavior, cognitive functioning and personality, all of which can result from TBI, also becomes barriers for persons with TBI to become successfully employed (14, 38). Cognitive deficits and personality change may have greater impact than physical impairment (18, 22, 41).

A combination of variables has been reported to increase the predictability of persons with TBI returning to work. These include: level of education, productivity status pre-injury, and overall functioning at discharge from acute rehabilitation (42); occupational category pre-injury (43); age, GCS score, and Disability Rating Scale score at rehabilitation admission (23); number of neuropsychological impairments (44); post-traumatic epilepsy, paralysis, visual field loss, verbal memory loss, psychological problems, and violent behavior (45).

Much of the prior research has focused on the symptoms and conditions of the individuals that influence returning to work. It is becoming more imperative to examine returning to work after TBI as an interaction between the needs and motivations of the individuals with TBI and the supports available within vocational, social and economic environments (46–48). Factors that lead to successful employment include socially inclusive work

environments and availability of health insurance (48), level of social interaction on the job and return to jobs with greater decision-making latitude (47), and environmental modifications and focusing on vocational strengths of the individual (46).

### Challenges in RTW

The preceding literature review indicates that investigators have typically focused on characteristics of individuals with TBI and the problems they exhibit, with a limited number of studies of the effects of workplace environment (e.g., Refs 47 and 48). However, it is important to realize that there are other influences on RTW that are often underestimated. Foremost among these is likely to be financial disincentives to RTW, such as when the individual is either pursuing or receiving public benefits such as Social Security disability benefits or other financial settlement. It is very likely that these individuals will be reluctant to pursue employment because they may believe that working negatively affect the financial well being of themselves and their families. This perception may seem contradictory and illogical, so some explanation is in order.

The Social Security Administration (SSA) administers disability benefits under two programs: the Disability Insurance (DI) program and the Supplemental Security Income (SSI) program. These two programs were designed to provide “safety net” levels of income and health care to individuals who are not capable of self-support due to disability. Unfortunately, SSI and DI are frequently cited as causes of high unemployment and underemployment of persons with significant disabilities. For example, *Bowe* (49) writes that these two programs are “dependence-oriented.” To be eligible, individuals who seek benefits must prove themselves to be incapable of engaging in Substantial Gainful Activity (SGA), currently determined by earnings of over \$800 per month. Fear of losing benefits, particularly medical coverage under Medicaid (typically tied to eligibility for SSI) or Medicare (tied to DI), persuades most beneficiaries to limit their earnings well below SGA or, more commonly, not enter the labor force at all. Further in this chapter, we will describe some of the ways in which SSA has attempted to counteract work disincentives and encourage their beneficiaries to attempt RTW. Understanding and accessing those work incentives is essential for convincing disability beneficiaries with TBI that attempting to return to work will not cause financial harm to themselves or their families.

In addition, a challenge that is common to many individuals across the range of disabilities is obtaining reliable and affordable transportation to and from work. This may be due to physical problems (i.e., vision, movement, etc.) that may preclude driving, lack of public transportation or paratransit services, or economic limitations

that come with long-term unemployment and high medical costs. Accommodations or alternative work arrangements, such as allowing the individual to telework from home, might be used to mitigate this barrier.

### THE CHANGING LANDSCAPE OF DISABILITY POLICY IN THE UNITED STATES

RTW services are delivered within a “landscape” of disability policy that defines such factors as eligibility criteria, types of services available, funding priorities and restrictions, mandates on providers and employers, and the rights and responsibilities of the recipient of services. Goodall and Ghiloni (50) present a thorough description of recent disability legislation in the United States that impact RTW for individuals with TBI, and brief summaries are provided in Table 61-1. We would like to focus on the most recent piece of legislation, the Ticket to Work and Work Incentives Improvement Act of 1999 because of the impact on Social Security Disability beneficiaries.

It is difficult to assess the participation in SSA disability programs by individuals with TBI because until recently SSA did not include TBI as a distinct impairment. SSA added TBI to its Listing of Impairments in August of 2000, and provided guidelines for disability assessment (51). The Listing of Impairments is used by SSA to determine if an individual’s impairments are severe enough to prevent

gainful activity. Because of this change, in the future it will be easier to estimate the numbers of individuals with TBI who receive SSA disability payments, engage in work activity while in disability status, and use Social Security’s work incentives. Within our own RTW program, nearly 100 percent of supported employment participants enter the program as SSI or DI recipients. It would be a logical assumption the participation of individuals with TBI in SSI or DI is high as well, and particularly for those who have the desire and motivation to return to work.

Hennessey (52) undertook an examination of the factors that influence successful attempts to sustain work effort by 1,003 SSA Disability beneficiaries. The following factors were found by Hennessey to be most significantly related to RTW:

- The individual had a financial need to work (81.8 percent of successful RTWs);
- The individual wanted to work (55.2 percent); and
- The individual’s health improved such that they could work (35.9 percent).

Other factors that were statistically significant included (a) knowledge of all the work incentives that were available to the beneficiary, (b) availability of job placement assistance, (c) flexible work scheduling as an accommodation, and (d) return to the same job and/or employer as before disability.

**TABLE 61-1**  
*Recent Disability-Related Legislation in the Individuals with TBI*

NAME	YEAR	MAJOR PROVISIONS
Rehabilitation Act Amendments	1986	Added supported employment as a service option for individuals with the most severe disabilities who require ongoing employment support.
Individuals with Disabilities Education Act (IDEA) Amendments	1990	Adds TBI as a specific educational disability; mandated school-transitional services for students beginning age 16.
Americans with Disabilities Act (ADA)	1990	Title I prohibits discrimination against individuals with disabilities in hiring, termination, promotion; also mandates reasonable accommodations for otherwise qualified individuals with disabilities.
Workforce Investment Act	1998	Designed to consolidate, coordinate, and improve employment, training, literacy, and vocational rehabilitation programs in the United States; funds One-Stop Career Centers for local service coordination.
Ticket to Work and Work Incentives Improvement Act	1999	Created the Ticket to Work program for SSA Disability beneficiaries; created national networks of authorized employment service providers and benefits advisement centers; strengthened several work incentives for beneficiaries.

Although this study is certainly not conclusive, it provides insight into the practicalities of RTW for SSI and DI beneficiaries. First, successful RTW is dependent on motivation to work, through intrinsic desire to be productive, financial demands, or both. Knowledge of work incentives under SSA programs can help beneficiaries overcome their initial fears about returning to the workforce and the risk of failure. Returning to a comfortable, supportive and accommodating work situation is also critical.

### Work Incentives

To remedy the concerns on the part of beneficiaries regarding employment and loss of benefit, Congress has enacted a number of work incentives for SSI and DI recipients (53, 54). Some of the more commonly used incentives are described in Table 61-2.

Increasing frustration with poor RTW within the SSI and DI programs led Congress to pass the Ticket to Work and Work Incentives Improvement Act of 1999 (TWWIIA, PL 106–170). This section will describe the enhanced Federal and State benefits programs and work incentives that either are or will soon be available to

individuals with TBI and other significant disabilities receiving SSI or DI.

**Benefits Planning and Assistance** TWWIIA establishes a community-based benefits planning and assistance program designed to provide accurate information on work incentives to SSA beneficiaries. SSA has funded entities across the nation to provide benefits planning and assistance, and conduct ongoing outreach efforts to inform beneficiaries of available work incentives. That program, the Benefits Planning, Assistance, and Outreach Program (BPAO), will increase opportunities for beneficiaries to receive information and services needed to become employed and perhaps attain self-sufficiency. Additional information about the BPAO program, including lists of BPAO projects by state, can be found at The Work Site along with information regarding all work incentives ([www.ssa.gov/work/](http://www.ssa.gov/work/)).

**Ticket to Work and Self-Sufficiency** The Ticket to Work and Self-Sufficiency Program is a voluntary program that is designed to allow SSI and DI recipients the opportunity to direct their own employment services and choose the services and providers they feel they need to initiate or

**TABLE 61-2**  
*Most Commonly Used SSA Work Incentives*

WORK INCENTIVE	AVAILABLE TO	DESCRIPTION
1619[a] and [b] Impairment	SSI recipients	These two options allow SSI/Medicaid recipients to retain either a cash benefit ([a]) or Medicaid coverage ([b]) for a period of time after achieving SGA.
Related Work Expenses (IRWE)	SSI and DI recipients	Certain expenses required for employment can be excluded from an SSI or DI beneficiary's earned income in determining monthly countable income. SSA must approve the work expenses.
Trial Work Period (TWP)	DI recipients	DI beneficiaries are given the opportunity to test ability to work without jeopardizing benefits. The TWP continues until a beneficiary accumulates nine months of work (not necessarily continuous work) in a rolling 60-month period.
Plan for Achieving Self-Support (PASS)	SSI recipients	Allows recipients to set aside income and/or resources to be used to achieve specific work goals. For example, money could be set aside for education, vocational training, transportation, or starting a business. The PASS must be approved by SSA.
Extended Period of Eligibility	DI recipients	Allows recipients to retain DI and Medicare eligibility while working.
Continued Payment Under a Vocational Rehabilitation Program	SSI and DI recipients	Allows for continuation of benefits while the recipient is engaged in Vocational Rehabilitation services.



return to work. SSI and DI recipients use a “ticket” or voucher to purchase needed services within an employment network, or EN. An EN can be a single provider agency, a one-stop delivery system, a group of providers that combines resources into a single delivery system, or even employers. If the individual enters and maintains employment above SGA, the EN will receive payment through one of two plans: (i) a fixed percentage of SSI or DI savings, or (ii) at achieved employment milestones.

Each EN in the ticket program serves a designated area and develops individualized work plans with beneficiaries from their service area who seek employment. A work plan will include statements of (i) the beneficiary’s vocational goal; (ii) services and supports necessary to reach the goal; (iii) terms and conditions related to the provision of supports and services; (iv) rights and remedies available to the beneficiary; and (v) the beneficiary’s right to modify the plan. Additional information about the ticket program is available at [www.yourtickettowork.com](http://www.yourtickettowork.com).

*Medicaid Buy-In* The Medicaid Buy-In provisions of TWWIIA address probably the most severe disincentive to employment of SSI or DI beneficiaries, the loss of health care coverage. Many, if not most individuals with significant disabilities will not enter the workforce in full-time positions with medical benefits, and therefore face the loss of health care when their earnings reach SGA. The Medicaid Buy-In component of TWWIIA will allow working individuals with disabilities (not just those receiving Social Security disability benefits) to purchase Medicaid services, just as if they were purchasing health care coverage through an employer-sponsored program.

A state can initiate a Medicaid Buy-In program through a relatively quick and simple amendment to its State plan that redefines eligible populations. This can be done through one or more of the following ways, such as raising income limits for eligible participants, disregarding earned or unearned income of the beneficiary or his/her spouse, or exempting certain assets (such as work-related assets).

In addition to the Medicaid Buy-In, TWWIIA allows working DI recipients to extend premium-free Medicare Part A (hospitalization) coverage for an additional 40 years beyond current limits, to a potential duration of 80 years, under certain conditions. Because each state defines eligibility and limitations for the Buy-In, the state Medicaid agency or local BPAO would be the best source to receive information about the options available.

*Other TWWIIA Incentives* TWWIIA contained two other major provisions that alleviate disincentives to work. Many beneficiaries are reluctant to attempt RTW out of fear that they would be unable to regain benefits should their physical or mental condition worsen and they would be unable to continue working. TWWIIA allows

an individual to receive immediate reinstatement of benefits that were terminated due to earnings. To be eligible for reinstatement, an individual must request reinstatement within 60 months of termination of benefits.

Another major disincentive was the potential impact of work on a Continuing Disability Review (CDR). CDRs are periodic reviews to determine if an individual’s medical condition has improved sufficient to terminate disability benefits. Any earnings reported to SSA might “trigger” a CDR before the individual is working at a self-sufficient level. TWWIIA addresses this concern by, first, disallowing CDRs for any beneficiary who is using a ticket, and second, disallowing CDRs triggered by work activity. CDRs that are regularly scheduled are allowed.

### CAREER DEVELOPMENT OF PERSONS WITH TBI

Career development theories have evolved during the last ten years and the pressure to address the needs of racial and ethnic minorities is making those more and more useful to people with disabilities. However, despite this fact, applicability of career development theories for people with disabilities remains a concern. Empirical research on the impact of disability on careers is at a relatively early stage. According to Szymanski et al. (55), outcome on career development for persons with disabilities has been strikingly similar to the study outcomes on racial and ethnic minority groups. Research has revealed that people with disabilities are underrepresented in the labor market and that certain contextual factors like education are related to employment. Outcomes have not indicated what mechanisms are involved in the career development of people with disabilities.

Szymanski et al. (55) also report, that there are some methodological problems inherent in studying the career development of people with disabilities. Various studies, and in particular those related to career indecision, have been plagued by poor design, conceptual ambiguities, methodological weakness, and low statistical power. Thus, it is not surprising that the data have resulted in conflicting findings. Even in light of these discouraging findings, career development theories can provide a conceptual framework that can be useful when providing career counseling to persons with disabilities. The key is to adjust the approach to the individual circumstances at hand (6).

Future research on career development for people with disabilities presents some interesting challenges. On the one hand, it is important to study this population due to their limited access to employment opportunities. On the other hand, it is important to recognize that there are inherent flaws in studying this or any population in isolation or in simple comparison with another group (33).

To better understand the career development of people with disabilities in a broader context future research should include people with disabilities and those from racial and ethnic minority groups in larger scale research. Qualitative research should also be considered to improve our knowledge of the complex interaction between disability and career development.

### Career Interest Assessments

Career assessment interventions are important tools that allow people with or without disabilities to take control of their career planning. The 1992 Amendments to the Rehabilitation Act emphasize consumer involvement in the rehabilitation process, including vocational assessment; self-rating instruments and interviews appear to provide the individual with the disability with more involvement over the assessment process. In this section we will review several types of interventions that were selected by the authors due to their availability and applicability for people with Traumatic Brain Injury (TBI).

Many career assessment tools are available on the Internet. One of the most popular career interest inventories is the Self Directed Search designed by John Holland. There are three versions one for adults, one for college students, and one for secondary school students and adults with limited reading skills. It is based on Holland's theory that there are six basic personality types: Creative, Realistic, Investigative, Artistic, Social, and Enterprising. The theory assumes that there are six corresponding work environments, and that individuals will find "person-environment fit" in work environments that most closely match their personality (56).

The Strong Interest Inventory may also be useful in assessing career interests of individuals from middle school through adulthood. The instrument reports a score for the six areas of interest described by John Holland, as well as 23 basic interest scales and 207 occupational scales. Myers-Briggs provides information on personality type, and will give added perspective to self-exploration exercises. Both the Strong Interest Inventory and the Myers-Briggs are online at Career By Design at [www.careers-by-design.com/](http://www.careers-by-design.com/).

The ability to reason is not a single process, but an extremely complex network of related processes. After a TBI, even simple tasks like completing an interest inventory, can require a great deal of thought. The inability to reason, make sound judgments and initiate, and plan or organize, may become virtually impossible, and this can affect a person's ability to independently perform career exploration activities. In such an instance a vocational specialist can provide the necessary support to enable the person to complete this type of activity.

Another popular career counseling strategy involves using computer assisted systems. These systems are able to handle vast quantities of information and assist with

integration of information (78). Many computer assisted career guidance (CACG) systems are available: CHOICES, SIGI Plus, and DISCOVER to name a few (57). These interventions provide individuals with current, accurate, locally relevant occupational, and educational information.

Discover is a computer program that assists people with self-assessment and provides information related to making career decisions. SIGI Plus is similar, however it does not provide information on postsecondary education. Choices should be used under the guidance of a vocational counselor. It helps the jobseeker learn more about abilities and interests and how they may relate to different careers.

Some persons with TBI may be able to use these tools with out assistance, while others may need help with reading, writing and interpreting the results. In addition, to learning more about vocational interests and aptitudes the opportunity to work through a career search exercise with a person with a TBI can also provide valuable information about current physical, cognitive, and social skills.

A number of career planning books are available to assist persons with identifying their skills and abilities. For example, Melanie Witt's book *Job Strategies for People with Disabilities* (58) contains a wide range of self-assessment tools to help a person define their career direction. Another career planning book, *Coming Alive from Nine to Five* by Betty Michelozzi provides a number of self-assessment exercises that may be useful to person seeking a first job or switching career tracks. Again, some job seekers with TBI may require assistance with completing the assessments, as well as interpreting the results and translating this data into useful career search information.

### Experiential Assessment

Work experience and similar interventions like volunteering or job shadowing may be useful for some people with TBI. If an individual has very limited experiences from which to make an informed career decisions, a work experience may help the person choose a career direction (55). Volunteering in various work settings may give some individuals with TBI ideas on abilities, preferences, and support needs. Job shadowing, can also serve this purpose. This strategy typically involves observing or "shadowing" a person who is performing a job. Some persons with TBI will need assistance with setting up and participating in either type of activity. A vocational rehabilitation specialist can assist an individual with contacting employers and making the necessary arrangements. Then while the activity is taking place, the vocational rehabilitation specialist can accompany the person to the jobsite and make notes on the person's likes and dislikes for certain types of jobs and work settings. This type of information can be very

valuable in the future when the person is actively trying to determine an initial direction for the job search or making decisions about whether or not to accept a job offer. Please note that neither of these activities should be viewed as a prerequisite to going to work, instead both are time-limited career exploration activities.

### **Home Visits**

Whenever a vocational rehabilitation specialist is involved with assisting a person with a TBI with locating work, a home visit can provide important vocational assessment and career search information. During the home visit the individual with the TBI is asked to share details on current abilities, work interests, and values. The person is also observed performing various tasks in their home environment, which demonstrates current physical, cognitive, and social skills. In addition, casual conversations about activities of daily living, tasks completed around the house, and leisure pursuits can also lead to some ideas on vocational abilities and interests (59).

### **Career Information Interviews**

This approach provides a valuable means for learning more about an occupation or industry. It involves setting up an appointment with someone in a particular field and interviewing the person to learn more about a specific occupation or industry. Some people with TBI may need assistance with setting up and conducting the interview. In this instance, a vocational specialist assists the person with determining the businesses to contact, making contacts, coordinating the interview, formulating questions to ask, and actually conducting the interview. The person with a TBI is encouraged to participate in each activity as much as possible. The vocational specialist should assist as needed and if present at the interview should take notes, as well as make observations of the individual's abilities. This type of exploratory interview offers the job-seeker information on minimal qualifications, education or training needed, for certain types of work. Information on how a particular career choice might impact future earnings and quality of life can also be gleaned from an informational interview (59).

## **VOCATIONAL ASSESSMENT**

### **Functional Assessment**

As mentioned earlier, through the years, traditional evaluation practices that use aptitude batteries, work samples, and behavioral inventories have dominated vocational evaluations for persons with severe disabilities. However, problems related to reliability and validity has demanded

that the process of assessment be conceptualized once more, so persons with disabilities are not being considered "too disabled" and unable to work. The traditional evaluation process is a linear process that identifies interests, abilities, and aptitudes at one point in time and assumes that this will not change overtime. Then these outcomes are used to predict subsequent learning, performance and success at work. Simply said, they focus on what someone cannot do rather than tuning in to the power of workplace accommodations and on the job supports.

Since many persons with severe disabilities like TBI enter the vocational assessment or evaluation process with limited marketable skills, they are likely to be excluded from work. Instead, they may be told that they need a longer recovery period prior to seeking work, or that they are not likely to ever work again and should be resigned to staying at home and collecting government benefits. In the worse case scenario, they are advised to enter programs to "get ready" to work, offered pre-employment training for menial jobs, sent off to day activity centers, or to work in an enclave. An enclave involves having a small group of people with disabilities working together in a community-based job, while under the constant supervision of a vocational rehabilitation specialist. For example, a group of five people may work as a team to clean a department store.

Traditional vocational evaluations occur in artificial and simulated environments, which are not reliable or valid indicators of what someone can do in the real world. There are a number of limitations in traditional approaches to vocational evaluation for persons with significant disabilities. The authors strongly believe that the most fair and reliable way to assess a person's abilities is within the context of real work environments. And furthermore they believe that the focus of a vocational assessment should be on interests, abilities, supports available, and supports needed to succeed at work.

### **Consumer-Focused Alternatives to Traditional Vocational Assessment**

An approach to career planning that is gaining more and more popularity, particularly in the medical community, are customized functional vocational assessments in real work environments (60). A functional vocational assessment provides a specific appraisal focusing on the needs, skills, and interest of the person within the context of future work environments.

This practical approach can provide valuable career development information to individuals with disabilities and particularly those with the most significant disabilities. All too often persons with severe disabilities are considered either too disabled to work or not ready for employment. This approach focuses on current strengths and abilities and the types of supports that will enable a

person to succeed in the workplace. Since the assessment is customized, the design depends upon the person's previous work history and any current employment options. If the individual was working at the time of injury the assessment may be geared toward examining one of the following options: Return to Pre-injury Employer (includes self employment) performing pre-injury job (with or without accommodation), or return to Pre-injury Employer with reassignment to a different position (with or without accommodation). If the person does not have the option to return to the pre-injury employer, but desires information on whether or not he or she can use a specific skill set in the workplace, a Residual Skills Assessment may be warranted. If the person has limited or no work history or has been absent from the workplace for an extended period of time then a Career Exploration Assessment may be conducted. No matter which approach is used it is important that the evaluator is knowledgeable of any work medical work restrictions in advance to planning the assessment approach. A brief description of each approach will follow.

### **Accommodation and Support Needs**

People with traumatic brain injury who are returning to work may need to perform their job in a different way or require modified workstations, compensatory strategies, or other accommodations or supports (61). In this approach a vocational rehabilitation specialist works closely with both the employer and employee to assess the person's vocational abilities by taking data on some specific vocational skill and if warranted recommend support strategies.

Once the person receives a release to return to work, the vocational rehabilitation specialist (with the employer's permission) accompanies the employee with TBI back to work and makes observations on the person's ability to perform the essential job functions. This criterion-referenced assessment measures the individuals' ability to do a specified task by collecting data on the steps of that task. Depending upon the nature and complexity of the job, other job-site personnel may need to be involved in planning and implementing the assessment. If difficulties arise, the specialist makes recommendations on ways to remove barriers and enhance independent performance.

For example, the returning employee and/or employer may need assistance with identifying and implementing accommodations like compensatory memory strategies. The return-to-work assessment is not used to determine whether or not someone can return to work but instead can provide ideas on types of possible accommodations and supports needed to enhance a successful return to work.

### **Residual Skills Assessment**

While some individuals may have work to which they can return to, others may not, but may have a keen interest in pursuing an employment opportunity that requires the use of his/her specialized skills, training, or educational background. In order to make an informed decision about whether or not to return to this type of occupation, the individual may need information on his or her current skills, abilities, and possible accommodations. A customized vocational assessment specifically designed to explore current level of functioning in a previous line of work and support needs may prove useful, and instill the confidence the person needs to return to this type of work. Sometimes the assessment may also relate to using one's educational background in the workplace and might help someone determine whether or not to pursue a career in a specific field.

Depending on the nature and complexity of the occupation in question, a consultant who is actively engaged in such work may be needed to assist with designing and implementing the assessment. The consultant should be someone who could be considered an "expert" in the field or area that is under exploration. The vocational specialist usually takes responsibility for locating and securing the consultants' service, coordinating the effort, assisting with the assessment design and tools, and writing a report. The specialist may also actively participate in the assessment process by making observations and collecting data on the individual's abilities and support needs.

### **JOB SEARCH AND EMPLOYER NEGOTIATION STRATEGIES**

Career development and planning are necessary first steps toward going to work and once a vocational direction has been established the job search should begin. As the search unfolds, the direction should be modified based on any new information that surfaces during this process. This section will review some of the issues that impact the job search and suggest strategies that may be useful when assisting persons with TBI with going to work.

### **Disability Issues**

According to a recent Louis Harris and Associates (77) national survey of people with disabilities, more than 71 percent of working age adults with disabilities are unemployed, despite the fact that two-thirds of these individuals want to work. Moreover, in 1992, an extensive national longitudinal study of students with disabilities who had exited schools found that the employment rates of individuals with disabilities lagged significantly behind those of their peers without disabilities (62). Other studies

confirm a continuing troublesome trend toward high rates of unemployment or underemployment for former recipients of special education services (63, 64).

These results suggest that the issue has never been whether or not persons with disabilities want to work, but instead has been on what is inhibiting their participation in the workforce. Several interrelated issues have made securing work a significant issue for persons with TBI. These include misperceptions and prejudice by employers, the general complexity involved in conducting a job search, and effectively representing one's abilities and support needs to an employer either during an interview or once hired.

Despite protections under the ADA, many people with disabilities remain unemployed. The law protects only qualified applicants or employees with disabilities. Some persons with significant disability may have a difficult time qualifying for an existing position or competing with all who apply for a given work opportunity. If an applicant or employee does not disclose that he or she has a disability he or she is not covered under the ADA. But at the same time, revealing this information may lead to being screened out of a job.

To avoid this conflict, it often pays to explore the "hidden job market". This requires learning about job opportunities before anyone else knows about them; these are the positions that are not being advertised. The best ways to tap into the hidden job market area by networking with personal contacts and contacting employers directly.

Individuals with TBI may have very limited personal networks due to social isolation (35). And in the instance where a personal network exists the individual may not be able to independently use his or her network to locate job opportunities. Memory problems can also make it difficult to manage the job search. For example, the person may not follow up for lead in a timely manner or may miss appointments with employers. Transportation can also be a problem. Some individuals may have difficulty getting to and from places of businesses without some assistance. Also, due to the myriad of cognitive problems that may result from a TBI some individuals may experience great difficulties with exploring occupations as well as conducting pre employment activities like completing employment applications, interviewing for a job, completing pre employment testing, and advocating for necessary on the job supports or accommodations.

It typically is the responsibility of the job applicant to best present his or her abilities to employers, and some people with TBI may have a difficult time doing so. Some individuals will not be able to explain to employers how their particular skills and abilities match the qualifications for the job. If the person is in need of an accommodation, he or she may experience difficulties explaining to the employer what is needed to allow him or her to

succeed. Some persons with TBI may need to convince an employer to redesign task, location, or restructure a job that was originally designed with individuals without disabilities in mind. This may present difficulties for the applicant with a TBI if he or she has a myriad of cognitive difficulties and is unsure of what he or she may need to succeed on the job. If the job seeker is unclear on how his or her abilities can best match an employer's needs, it is unlikely that a job offer will surface.

Sometimes, employers may not see a "new or different" way to get a task done or may see the request for change as bothersome. Instead the company representative may simply choose to hire someone else who does not require any accommodation. On the other hand, many employers may be willing to hire individuals with TBI, but may need support to determine how best to make reasonable accommodation. Vocational rehabilitation specialists can be a valuable resource for employers in this area.

Vocational rehabilitation usually offers a range of job search and placement services, from the least to most intrusive approach. The approach selected generally depends upon the individual's abilities and support needs. We will review a couple of these approaches and then focus in on what the author's view as the most favorable strategy for assisting persons with severe TBI with gaining employment; a customized and tailored approach to this process.

### **Minimal Intervention**

The first approach generally involves a minimum amount of intervention from a vocational rehabilitation specialist. For example, the jobseeker may simply need information on the labor market, insights concerning their interviewing skills, or leads on employment opportunities. Or perhaps the person simply needs information on adaptive aids or effective compensatory strategies. These individuals often know what they want, but need specific information to put their plan in to action. They may have previous work history and have a good work ethic. These individuals are usually able to read, write, and can follow through on complex directives without assistance. They take the information given to them, generalize it, and apply it to their lives. There need for vocational assistance is often minimal. Unfortunately, vocational rehabilitation professionals, who are unfamiliar with TBI may feel that a person with an injury is much more capable than he or she truly is and may only offer minimal job search and placement assistance. Afterwards, in instances where the person does not follow through on specific directives this may be perceived, by the vocational rehabilitation provider, as a lack of motivation to work on the part of the individual with TBI and in some instances may lead to termination of services.

### **Education and Preparation Approach**

The second vocational placement approach is for those individuals who appear to need some type of intervention, but not an extensive intervention. Usually, these individuals do not assimilate information quickly, and require assistance with carrying out a job search, but once employed may need no or limited assistance on the job. Often times, these individuals participate in classes designed to get ready or prepared for conducting either an independent job search or a job search with some limited assistance from a job placement specialist. This approach is usually not very effective for persons with significant TBI since most of the training takes place in a classroom type setting. Usually classes are conducted to teach job seeking and maintenance skills. For instance students learn about various occupations and how to analyze themselves and the job market to choose an appropriate career path, or receive information on how to complete employment applications or learn how to interview for a job.

Sometimes, particularly for persons with severe TBI, an inordinate amount of time is expended trying to get the person ready to conduct a job search, when in reality it is highly unlikely that the learning that takes place in the classroom will ever generalize into the real world. Instead, the authors feel that time could be better expended by providing individualized job placement assistance that is tailored to each job seekers specific needs and abilities.

### **Customized Approach**

This approach can be helpful to anyone with a disability, but is particularly useful for people with more severe disabilities like TBI. Using this strategy the type and intensity of services and supports are adapted to each individual's needs and under some circumstances involve extensive intervention. Generally, individuals with significant cognitive impairments need more assistance with obtaining employment than those who have moderate physical or sensory disabilities. These individuals tend to learn best in the milieu where they will be expected to perform instead of learning away from that environment. Generally, they need one to one assistance with identifying their vocational strengths, support needs, and conducting a job search. Once employed, they may need assistance on the job. One vocational service option that offers individualized and intensive support services for both gaining and maintaining employment is Supported Employment. This approach encourages full inclusion of the person with the disability in his or her job search and offers reality-based activities. A person does not have to get ready to work instead a vocational support person sometimes called a job coach provides assistance with helping the person identify his or her abilities and support needs, contact

employers to discuss hiring needs, and offers on the job assistance and long term follow along. This service option will be discussed in more detail in the next section.

## **WORKPLACE SUPPORTS**

No two individuals with TBI are alike, nor are their abilities or disabilities similar. Add in the different types of occupations and the huge variances within work environments and you have a totally unique situation on hand. Therefore, individuals with TBI who are attempting to return to work will need supports that are customized to meet their individual needs at a specific workplace. The type, level, and intensity of support will vary depending on the person's abilities and the particular circumstances on hand. Some individuals with TBI may simply need information and guidance on how to conduct a job search or ways to compensate for memory deficits on the job, while others particularly those with severe disabilities will need more intensive intervention and one to one assistance. Furthermore, the type, level and intensity of support someone will need, does not remain static, but changes over time. For example, after learning how to do a job task, the individual may need additional instruction when new duties are introduced. Individuals with TBI, may benefit from a combination of workplace supports. Some examples follow. For example, someone who has a job to return to will not need assistance with locating a new occupation, however once back to work he or she may need assistance with learning how to get organized and manage their workload.

### **Accommodations**

Some people with TBI will benefit from accessible building, particularly if the person has difficulty walking or uses a wheelchair for mobility. For example, a wheelchair lift was installed outside of the entrance of an inaccessible older historical building that allowed the employee who uses a wheelchair access. Those who have changes in vision post injury may also benefit from access supports. For example, raised letter directional signs may be posted in a building to help an employee identify restrooms or elevator controls.

A modified work schedule that allows an employee to get to work on time may also be necessary. For example, a person may be allowed to work 10 a.m. to 6 p.m. rather than 9 a.m. to 5 p.m. due to limitations on the availability of transportation to and from work. In other instances a person may need part-time work due to changes in one's stamina level or an increase in fatigue. Other people with TBI may be able to work full-time, but may need to have an opportunity to take additional scheduled breaks throughout the workday.

Job restructuring is another important accommodation. This involves having a non-essential (not major) work function or a marginal duty removed from an employee's job description or a difficult task that the employee cannot do is exchanged for one that can be done. For example, a general worker at a retail store is not able to climb ladders to change the light bulbs. Management agrees to allow another employee to do this and in exchange the worker is responsible for checking the parking lot and returning customer carts to the building.

Sometimes, particularly if the person has a physical disability or slowed movements post injury it will be useful to purchase assistive equipment or devices to improve their ability to get the job done. More often existing items in the workplace may be modified or added on to accommodate the person. Assistive technology ranges from high tech to no tech, costly to no cost. Fortunately most auxiliary aids are not expensive.

For some individuals a change in where their work is performed may be helpful. This may simply involve allowing the employee to move to a different workstation or in some instances and if applicable allow telecommuting or working from home.

Some individuals with TBI may need support services. Examples of support services may include assisting the person with carrying out activities of daily living like eating or going to the restrooms, having a "buddy" assigned to alert the worker to an emergency situation, or helping the individual take notes during an employee training, or staff meeting.

Perhaps one of the most useful accommodations for workers with a TBI are internal or external compensatory strategies. Internal strategies require the use of a mental support system and do not rely on external devices. Examples include, making associations or drawing on analogies to remember how to do a task or using word mnemonics to remember a specific sequence. External strategies involve the use of objects like checklists or flowcharts to remember a sequence of steps to follow to complete a work activity. These strategies can serve multiple purposes. They not only promote learning, but can also serve as a reminder of what needs to be done and helps keep the worker organized, so the job can be completed in a proper and timely manner.

It is important to remember that all workplace supports and adaptive solutions that are used to compensate for functional limitations are highly individualized. In addition, the solution to the presenting problem will be highly dependent upon the user's willingness to use a strategy, as well as, the type of job tasks involved, the work environment, and the employers' consent to allow the use of the accommodation. Although, these examples were presented in isolation it is often the unique interplay and right combination of supports that will lead to success at work.

Table 61-3 below provides some examples of the types of workplace strategies used by employees with TBI, who used a Supported Employment approach to assist them with going to work post injury.

Sometimes there are existing cues in the workplace that the new employee can learn to attend to that will promote successful job performance. Consider the following examples, a landscaper who is required to mow the lawn in a large office complex, is given a diagram on a daily basis that illustrates what areas are to be cut that day. A patient transporter works in a hospital that has different colored signage that helps him find his way to the correct destination. A medical supply order puller receives a printout indicating where in the warehouse the items needed are located.

In other instances the necessary support will be simple ergonomic modifications to the workstation or a change in the way the work is performed. This might include adapting the layout of a workstation so that the task can be better sequenced, raising a worktable to accommodate a wheelchair or customized seat, or using jigs or adaptations to mitigate the employees limitations in vision, dexterity, judgment, etc.

### **Job Coaching**

Most individuals with severe traumatic brain injury will need assistance with locating work, as well as assistance learning how to perform the job. One approach that has successfully been used to assist people with TBI with going to work is supported employment (4, 41). Using this approach a vocational rehabilitation specialist known as an "employment specialist" or "job coach" provides one to one individualized assistance to assist a person with a severe disability with finding a job, and once employed provides or facilitates the supports needed to help the person succeed at work. The type, level, and intensity of support varies depending upon the newly hired employee's abilities, the job, the work environment, existing supports in the workplace. Table 61-4 provides a brief overview of the role of the employment specialist, the person with a TBI, and other return to work process team members.

The level of involvement of the rehabilitation team will vary depending upon the time post injury and who is currently following the individual when he or she goes to work. The authors advocate for return to work as soon as possible. If a person has a job to return to it is important that some member of the team or family member act as a liaison with the employer to keep them abreast of the individual's progress in rehabilitation. In some instances the person may not be able to return to the same job, but there may be some other type of work within the organization. Some people maybe able to begin to return to work while involved in day rehabilitation on a part-time

**TABLE 61-3**  
*Examples of Workplace Supports*

<b>POSITION TITLE</b>	<b>JOB-RELATED FUNCTIONAL LIMITATION</b>	<b>PRESENTING ISSUE</b>	<b>WORKPLACE SUPPORT</b>
Receptionist at small business	No use of arms or hands, unable to walk	Taking messages on the telephone	Tape records voice messages then uses voice activated software to type messages
Garment bagger at dry cleaners	Unsteady gait, loss of balance while walking or standing; becomes tired easily	Pulling bags over cleaned garments from a standing position; maintaining stamina	Fabricated metal stand to maintain balance while standing; has flip down seat to rest on when tired
Inventory clerk/order puller for retail store	Becomes frustrated when interrupted and yells at others	Appears angry when new coworkers ask for instructions on how to do the job	Created oversized document to refer new employee's questions
File clerk at insurance company	Becomes defensive or denies having any difficulty when given personal feedback	Appears angry when given constructive feedback on job performance	Uses self monitoring tool and discuss ways to improve performance
Cashier for fast food company	Socializing with strangers in an appropriate manner	Asked customers for their telephone numbers	Posted reminder "Don't creep me out" with picture of unhappy looking female on the phone
Activities assistant at nursing home	Remembering sequence of things to be done throughout the day to complete normal routine	Could not remember what order to complete various job duties	Organized master schedule of various duties to complete on certain days and a list of things to do once duties are done
Plant installer at green house/plant retail store	Remembering how to complete a certain task	Could not remember how to clean and care for various types of plants	Created manual with instructions and cross referenced by plant typical and phylum name
Houseman at hotel	Remembering what to do outside of normal routine	Could not remember what tasks to do outside of normal work routine	Manager on duty writes daily list of things to do in order of occurrence

basis. Some people will not have a job to return to or were unemployed at the time of injury. These individuals will need to seek new employment.

Again the composition of the team will vary depending upon a number of factors. For instance, if the person is involved in or has recently completed out patient rehabilitation the team is likely to be made up of the individual with a TBI, a physiatrist, an occupational therapist, a physical therapist, a neuropsychologist, a social worker, the parents or significant others, a state vocational rehabilitation counselor and if supported employment is being used, an employment specialist or job coach.

Over the years business have become more confident in their ability to manage a diverse workforce and more cognizant of the abilities of workers with disabilities. Also, with the passage of the ADA, larger companies are more open to making reasonable accommodations in

the workplace. Thus, individuals who lack access to Supported Employment may still be able to achieve success at work, by simply working with the pre-injury employer or by seeking out flexible and accommodating employers.

### **INTERNATIONAL PERSPECTIVES**

This chapter has focused largely on RTW programs, supports, and legislation within the United States. However, many of the European and other developed countries have well-established neurotrauma and neurosurgical management for traumatic brain injury (e.g. Refs. 65–69). These countries have comprehensive rehabilitation programs in place, with the emphasis on comprehensive interdisciplinary rehabilitation program that includes therapy to overcome the disability which are caused by physical,



**TABLE 61-4**  
**Overview of Supported Employment Services and Roles of Interdisciplinary Team Members**

EMPLOYMENT SPECIALIST	INDIVIDUAL WITH TBI	OTHER TEAM MEMBER ROLES
<i>Supported Employment Activity:</i>		
Getting to know one another and establishing a direction for the job search		
<ul style="list-style-type: none"> <li>• Conducts functional community based activities to get to know the jobseeker and observe current skills, abilities and potential support needs;</li> <li>• Interviews those who know the person best to determine the above;</li> <li>• Identifies jobseekers personal support network;</li> <li>• Discusses impact of earnings on benefits;</li> <li>• Discusses disclosure issues;</li> <li>• Provides feedback to others (i.e. family, team and funding source)</li> </ul>	<ul style="list-style-type: none"> <li>• Becomes familiar with service option;</li> <li>• Gets to know the job coach;</li> <li>• Participates in activities to learn more about self and job market;</li> <li>• Expresses needs and wants related to employment;</li> <li>• Decide who will disclose disability to potential employers.</li> </ul>	<ul style="list-style-type: none"> <li>• Makes referral and introductions to SE;</li> <li>• Advocates for SE services with funding source if needed;</li> <li>• Shares information, current records, and insight on a person's abilities and support needs;</li> <li>• If returning to pre-injury job, is liaison between employer and SE provider;</li> <li>• Provides insight on family dynamics;</li> <li>• Develops questions for neuropsych evaluation and or assessment.</li> </ul>
<i>Supported Employment Activity:</i>		
Conducting the job search, applying for jobs and interviewing		
<ul style="list-style-type: none"> <li>• Locates work opportunities by tapping in to the hidden or unadvertised job market;</li> <li>• Meets with employers to describe SE services and job seeker's desires and abilities;</li> <li>• Analyzes workplace and job to determine pros and cons that may impact success at work and long term job retention;</li> <li>• Discusses above with job seeker;</li> <li>• Practices interviewing skills;</li> <li>• Arranges interviews;</li> <li>• Helps negotiate accommodations;</li> <li>• Provides feedback to others (i.e. family, team and funding source)</li> </ul>	<ul style="list-style-type: none"> <li>• Uses personal network and other resources to identify businesses to contact;</li> <li>• Decides whether or not to learn more about a work opportunity;</li> <li>• Completes applications for employment;</li> <li>• Attends job interviews;</li> <li>• Decides whether or not to accept job offer.</li> </ul>	<ul style="list-style-type: none"> <li>• Shares ideas on employers to contact;</li> <li>• Provides ideas on types of tasks or jobs that may maximize use of personal strengths;</li> <li>• Reviews job descriptions and provide release for work if needed;</li> <li>• Makes suggestions on types of accommodations or strategies that may prove useful;</li> </ul>
<i>Supported Employment Activity:</i>		
Providing ongoing long-term job retention services.		
<ul style="list-style-type: none"> <li>• Stays in touch with employer and employee to assist with any additional training needs or help resolve difficulties in the workplace;</li> <li>• Collects data on performance levels;</li> <li>• Provides additional services as indicated</li> </ul>	<ul style="list-style-type: none"> <li>• Asks for assistance if needed;</li> <li>• Expresses job satisfaction;</li> <li>• Helps problem solve.</li> </ul>	<ul style="list-style-type: none"> <li>• Helps problem solve.</li> </ul>
<i>Supported Employment Activity:</i>		
Providing or facilitating off the job support case management services.		
<ul style="list-style-type: none"> <li>• Assists with problem solving issues outside of work that if left unaddressed could adversely effect work;</li> <li>• Makes referrals to other resources</li> </ul>	<ul style="list-style-type: none"> <li>• Identifying problems outside of work that are effecting performance;</li> <li>• Helps problem solve</li> </ul>	<ul style="list-style-type: none"> <li>• Provides resources;</li> <li>• Makes referrals to other resources</li> </ul>

communicative, cognitive, and behavioral impairments, providing assistance in community integration in terms of living situation, productivity, and social and recreational activities, and providing psychosocial support for patient and family members (e.g., Refs. 8, 23, 70, 71).

The importance of RTW after injury is being recognized, and these rehabilitation programs also offer similar types of vocational assistance, such as work trials, training at workshops, or work training organized on the open job market. However, some programs limit the provision of vocational rehabilitation to those who are eligible in terms of capabilities. For example, Rehab UK assesses the abilities and potential of the applicants before accepting them into the program, offering vocational rehabilitation opportunities only to those who have good cognitive skills (72).

In the developing countries, challenges that individuals with TBI are faced with are further magnified due to either short supply or unavailability of rehabilitation professionals, in addition to lack of service centers to cater for their requirements (73–75).

### IMPROVING FUTURE OUTCOME THROUGH A TEAM APPROACH

Traumatic brain injury (TBI) results in disability that requires comprehensive and often lengthy rehabilitation efforts. It is expensive from the standpoint of rehabilitation costs, lost earnings, and therefore, loss to the gross national product, but moreover, costly due to human suffering. Although healthcare and vocational rehabilitation professionals are continually challenged in their efforts to return individuals with TBI to work, the likelihood of successful vocational rehabilitation for persons with traumatic brain injury can be enhanced by utilizing a team approach (76). Key members of the return to work team include the person with TBI; significant others; the employer; neuropsychologist; occupational, speech, and physical therapists; social worker; and vocational rehabilitation counselor or specialist often under the leadership and direction of a psychiatrist. Through interdisciplinary collaboration, the team can communicate frequently and set mutual treatment goals for recovery.

The task before the team is to maximize the potential of the individual with brain injury to return to as high a level of pre-injury productivity as can be achieved. Further efforts related to return to work might focus upon establishing new and different life goals and activities. The overall goal of rehabilitation, therefore, involves an enormous effort on the part of both the survivor and rehabilitation team.

While there is no typical length of TBI rehabilitation, there is often a long and arduous process of treatment and therapies that assist the person with returning to pre-injury

lifestyles, including work. Much depends on the severity level of the TBI, the nature and extent of problems, availability of social support networks, accessible and available appropriate rehabilitation, and the circumstances surrounding re-employment and the current labor market. Fewer individuals return to work at the same level, for the same pay, and at the same number of hours per week as before the injury. Some return to a similar job at a full-to part-time level, with a reduced rate of pay, others do not pursue competitive employment. Psychosocial outcomes encompass a similar range, from those being able to resume a familiar social and family life to those who become divorced, separated, or experience shrinking social networks and eventual isolation.

In the best-case scenario, a psychiatrist will be integrally involved in and oversee the team efforts to assist the person with the returning to work. And once employed, the psychiatrist and other team members continue to assist with either an advisory role or on an as needed basis.

As mentioned earlier, a neuropsychological evaluation is often used to assist in planning for employment or re-employment. A sound evaluation can provide valuable data to use when determining occupations or work settings that may be more suitable for the person with TBI to consider. The results of a good evaluation can help the person with TBI and team determine the best fit between cognitive assets and deficits, behavioral functioning, interpersonal propensities, overlearned skills or old learning ability, with specific job tasks and work environment for the person with TBI. The results can generate probability statements about the type of job, sort of tasks that may be most appropriate, as well as the types of environmental factors, and supports that may promote the person's success at work.

However, the relationship between neuropsychological test scores and the demands of daily life can be weak. These is why the evaluation should include more than just testing, but also involve gathering other relevant historical, medical, psychosocial, and vocational information from the person, significant other, and team members.

The return to work team can make suggestions on what specific information needs to be obtained from the neuropsychological evaluation and provide other relevant information. For example, inquiring about the personal assets can often be more helpful than dwelling on what the person is unable to do, particularly when planning for a return to work. Also, whenever deficits are mentioned, asking what areas are amenable to remediation and to what extent training or supports can contribute to change is critical. For example, the neuropsychologist may be able to state functions that are expected to improve due to spontaneous recovery or can be assisted by compensatory strategies or other means like job restructuring or environmental modifications.

The use of simple assistive technology is often pivotal to a successful return to work. Technology can help eliminate difficulties in physically accomplishing work activities or improve cognitive functions, like the ability to attend, organize, sequence, and evaluate the result of work activities. Often the process and effort involved in identifying an appropriate intervention can be more involved and costly than the intervention itself. Thus, consultation with experienced team members is very important, as it can not only expedite this, but enhance probability of success.

Using assistive technology at work may be the first time the person is offered assistance that does not appear to be typically clinical. Such interventions are often very empowering and can contribute significantly to the person's ability to be productive at work, as well as more effective in other activities of daily living.

A TBI interferes with a person's identity and social roles. The results of the injury and particularly the inability to work often disrupt a person's sense of purpose, productivity, and self-worth. Therefore, counseling may prove beneficial and help a person with reestablishing a satisfactory level of self-sufficiency. Also, after returning to work, the individual may experience depression or increased frustration at not being able to do things as easy as pre-injury levels. Furthermore, not being accepted by peers or rejection from coworkers can lead to problems. In some instances counseling may be warranted, in others medication may be helpful. The psychiatrist can recommend interventions to assist here. As illustrated, the role of the team, under the direction of a physiatrist, cannot be over emphasized (76). Unfortunately, however, in some instances, a physiatrist may not be accessible. In such an instance a competent general medical practitioner, who is willing to consult with a physiatrist, can lead the team.

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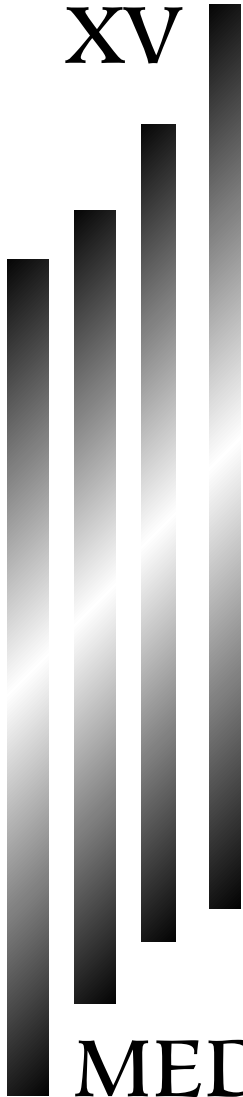
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XV



**MEDICOLEGAL AND  
ETHICAL ISSUES**

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# 62

## Medicolegal Aspects of TBI

*Irvin V. Cantor*

### INTRODUCTION

According to the Brain Injury Association, each year at least 1.5 million Americans sustain a traumatic brain injury (“TBI”). TBI has been called “the silent epidemic” of our society. Associated with this epidemic is a myriad of legal issues specific to persons who have sustained TBIs and their families. Since it would be far too ambitious a task to analyze all of these legal issues in the space available, this chapter is intended as a basic outline and discussion of some of the pertinent medicolegal aspects of TBI.

### SPECTRUM OF MEDICOLEGAL ISSUES OF TBI

There exists a vast array of traumatic brain injuries in our society. The contexts in which TBIs may arise are many, including motor vehicle collisions, recreational accidents, watercraft accidents, workplace accidents, defective products, and medical malpractice. The injury to the brain may be mild, moderate or severe. The mechanism of injury to the brain may involve blunt trauma, acceleration—deceleration of the head, or a metabolic process which may result in hypoxic or ischemic insult to the brain. TBIs may cause physical, cognitive and emotional dysfunction. Unlike most other injuries to the human body, an injury to the brain may not be noticeable to others. All of these

factors result in an enormous spectrum of medicolegal issues.

The issues discussed in this chapter are intended to reflect a basic and broad discussion of the medical legal aspects of TBI:

1. Finding the Right Attorney
2. Competency and Capacity Issues
3. Right To Die and Do Not Resuscitate Laws
4. Anatomy of a Worker’s Compensation TBI Case
5. Anatomy of a Personal Injury TBI Case
6. Anatomy of a Medical Malpractice ABI Case
7. Independent Medical Examinations
8. Expert Witness Testimony in a TBI Case
9. Lay Witness Testimony in a TBI Case
10. Demonstrative Evidence in a TBI Case
11. Protection and Preservation of the TBI Client’s Recovery After Settlement, Verdict, or Award

There are several books which have been written on the subject of the legal aspects of TBI, which provide a detailed discussion of many of the issues addressed in this chapter (1–4).

### FINDING THE RIGHT ATTORNEY

Traumatic brain injury litigation is one of the most complex areas of trial law. It requires a working knowledge



of the anatomy and function of the human brain combined with an understanding of how best to present evidence to prove or disprove the mechanism, nature and extent of the TBI. In recent years, there has evolved the field of neuro-law, comprised of trial lawyers who have training and experience in traumatic brain injury litigation. It is usually advisable for someone seeking legal help for a TBI to seek out an attorney who has knowledge and experience in handling such cases.

The context of the TBI is a key element in finding the right attorney. The four primary areas of law involving TBI litigation are: (1) Personal injury, where the injury was caused by a motor vehicle or other type of accident; (2) Worker's Compensation, where the injury occurred in a workplace accident; (3) Medical Malpractice, where the injury was due to the negligence of a hospital, physician, or other healthcare provider; and (4) Products Liability, where the injury was due to the use of a defective product. Generally speaking, trial attorneys specialize in one or more of these areas of law. However, just because an attorney regularly handles TBI cases stemming from motor vehicle collisions, for example, does not mean he or she has any experience with worker's compensation or medical malpractice cases. It is almost always advisable for the person seeking legal help to choose an attorney who specializes in the particular area of law in which his or her case arises.

The best way to locate the right attorney is often to seek referrals from healthcare professionals who regularly are involved in TBI litigation or others who are knowledgeable of those attorneys in the community who regularly handle TBI cases. The Brain Injury Association of America (5), the statewide brain injury associations and the local brain injury associations, are also excellent referral sources. The Brain Injury Association of America publishes a book, *National Directory of Brain Injury Rehabilitation Services*, which lists attorneys who regularly handle TBI cases in each state in the United States (6). Likewise, the American Trial Lawyers Association (ATLA) (7) and the statewide and local trial lawyers associations often will provide names of attorneys who regularly handle TBI cases. Martindale-Hubble, a national legal directory which lists attorneys in every locality in the United States, includes information about the attorney and his or her areas of practice, including TBI litigation and neurolaw (8).

Most importantly, the person seeking legal help for his or her TBI case must feel comfortable and confident with the attorney chosen. TBI litigation is often a long, tedious and uncomfortable process, in which a strong relationship between the client and the attorney is invaluable.

## COMPETENCE AND CAPACITY ISSUES

Issues involving competency and capacity often arise following traumatic brain injuries. Cognitive dysfunction

caused by injuries to the brain may range from mild problems with attention, concentration or memory, at one extreme, to being in a comatose or vegetative condition, in the other extreme. Consequently, it is important to determine the ability of the person who has sustained a TBI to understand and comprehend the consequences of his or her actions.

"Competency" generally refers to someone's ability to perform an act or understand the consequences of an act. "Capacity" is generally a legal term, describing one's adjudicated ability to perform an act or form an intent regarding an act. The adjudication of incompetency by a court determines one's capacity. This adjudication is issue specific, limited to only those acts or actions which the person is unable to do or comprehend. For example, one may be adjudicated incapacitated to handle his or her own financial affairs, but fully capable of making his or her own decisions about medical care. The law is designed to protect incompetent individuals. Minors under the age of 18 are generally deemed incompetent. Adults are presumed to be competent. In the author's home state of Virginia, Virginia Code Section 37.1-134.6 defines "Incapacitated Person" as:

. . . an adult who has been found by a court to be incapable of receiving and evaluating information effectively or responding to people, events, or environments to such an extent that the individual lacks the capacity to: (i) meet the essential requirements for his health, care, safety or therapeutic needs without the assistance or protection of a guardian or (ii) manage the property or financial affairs or provide for his or her support or for the support of his legal dependents without the assistance or protection of a conservator. A finding that the individual displays poor judgment, alone, shall not be considered sufficient evidence that the individual is an incapacitated person within the meaning of this definition. A finding that the person is incapacitated shall be construed as a finding that the person is "mentally incompetent . . . [for the acts and actions listed in the court's order]."

Health care providers often treat TBI patients who are obviously incompetent, but have not yet been adjudicated incapacitated. In these situations, the patient's next of kin are typically vested with the statutory authority to make health care decisions for the patient. This surrogate decision-making by family members is usually the determinative factor when it comes to decisions involving do not resuscitate orders or terminating life support efforts.

Attorneys who are requested to represent the interests of the TBI patient must be sure the patient is competent to manage his or her affairs. If not, the attorney must quickly take steps to have the patient adjudicated incapacitated and have a legal fiduciary appointed. Only the duly appointed fiduciary has the authority to actually

engage the attorney to represent the incapacitated person. Additionally, since the fiduciary may serve as the patient's surrogate for medical decisions, the attorney should advise the patient's family of the applicable right to die and related medical decision—making statutes.

One commonly overlooked area of TBI litigation is the competency of the TBI litigant to manage any funds recovered as a result of the litigation. It is not uncommon for the TBI litigant to be fully competent to hire counsel, initiate a lawsuit, and make his or her own medical decisions, yet be incompetent to manage his or her financial affairs. In such situations, the attorney must be careful to have a court order the proper disposition of the funds. Typically, this will result in the court having the funds placed in trust for the TBI litigant.

### RIGHT TO DIE AND DO NOT RESUSCITATE LAWS

When someone suffers a catastrophic brain injury, there are tremendous consequences not only to the patient, but also to the family, the healthcare providers, and many others who have a connection to the patient. Hopelessness, futility, and despair are common emotions felt by these persons. In this framework, ethical and moral dilemmas abound.

There is a wide disparity of recovery after severe brain injury, ranging from the person who substantially regains his or her pre-morbid level of functioning to the person who has remained in a vegetative state for a prolonged time. Moreover, predicting outcome after traumatic brain injury can be difficult. Consequently, extreme caution should be employed by those who consider the quality of the patient's life and issues involving the patient's right to die.

One's quality of life is a personal and subjective determination. Obviously, the patient's awareness of his or her environment is a key factor in this determination. In patients in permanent vegetative state, questions arise on both personal and societal levels. Should the patient be kept alive by artificial means or be allowed to die? Does it make sense to continue to provide the enormous costs necessary to keep the patient alive or should our limited societal resources be used for others who have a better medical and functional prognosis? Such questions have also come up in legal challenges involving patients in a minimally conscious state, where there is clearly more ethical debate in the medical community at large regarding issues of medical futility. Non-vegetative patients who demonstrate low level neurobehavioral response, such as those in a minimally conscious state ("MCS"), by definition, have some level of awareness. Such severe disability may seem like a poor quality of life to one person, but quite acceptable to another person given the potential of

death. Consequently, decisions to allow MCS patients to die are extremely emotional, controversial decisions to make.

One significant area of debate in vegetative state cases is whether or not a patient should be made a "DNR" (do not resuscitate), and if so, when. There actually exists a continuum of medical orders which will and/or could result in death to the patient in VS: (1) do not resuscitate orders ("DNR"); (2) withholding medical treatment such as antibiotics or surgery; (3) removal of a feeding tube; (4) removal from a respirator; and (5) withholding or withdrawing other life sustaining care, noting that withdrawing care reaches a greater level of potential moral and ethical compromise than withholding care. The decision to take such actions, first and foremost, belongs to the patient, and if the patient is incapable of making an informed decision, or had no advance directive, then to his surrogate, usually his family. Most states have laws regarding one's right to die based upon the person's living will or advance directive, such that any decision to withhold or withdraw medical treatment is based upon the patient's previously expressed preferences. Most states further provide that the attending physician may withhold or withdraw medical treatment upon compliance with the applicable state law and the proper authorization of the patient's surrogate. In the author's home state of Virginia, Va. Code Section 54.1-2986 enumerates an order of priority of persons who may be such surrogate, beginning with the patient's guardian or committee and then to the patient's next of kin. The Virginia statute dictates that where the patient has not previously expressed a preference regarding withholding or withdrawing medical treatment, the surrogate "shall (i) prior to giving consent, make a good faith effort to ascertain the risks and benefits of and alternatives to the treatment and the religious beliefs and basic values of the patient receiving treatment. . . and (ii) base his decision on the patient's religious beliefs and basic values and any preferences previously expressed by the patient regarding such treatment to the extent they are known, and if unknown or unclear, on the patient's best interests." Va. Code Section 54.1-2986(A). Virginia Code Section 54.1-2987.1, Virginia's Durable Do Not Resuscitate Order statute, provides, among other things, that a physician may issue a durable do not resuscitate order "for his patient with whom he has a bona fide physician/patient relationship as defined in the guidelines of the Board of Medicine, and only with the consent of the patient or, if the patient is a minor or is otherwise incapable of making an informed decision regarding consent for such an order, upon the request of and with the consent of the person authorized to consent on the patient's behalf".

In *Cruzan v. Director, Missouri Department of Health*, 497 U.S. 261, 110 S. Ct. 2841 (1990), the U.S. Supreme Court stated that a person has a constitutionally

protected right to refuse lifesaving medical care, including hydration and nutrition. With regard to an incompetent person, such as Nancy Cruzan who was presumptively in a vegetative state (although experts on the two sides debated this), the State of Missouri had a statutory scheme which allowed a surrogate to elect to withdraw hydration and nutrition and thus cause death upon clear and convincing proof that such withdrawal was what the incompetent desired. The Supreme Court upheld the statute as constitutional in a case where the surrogates, Nancy Cruzan's parents, requested withdrawal of hydration and nutrition, but failed to meet the clear and convincing standard embodied in the Missouri statute. In a dissenting opinion, Justice Brennan argued that the incompetent should not have such "improperly biased procedural obstacles" preventing her from dying with dignity. *Id.* at 302. He pointed out that "Missouri is virtually the only state to have fashioned a rule that lessens the likelihood of accurate determinations" because of its heightened evidentiary standard. *Id.* at 326.

Virginia, like most other states, has a statute which does not contain a heightened evidentiary standard such as Missouri's statute, which was the subject of *Cruzan*. Rather, Virginia's statute simply provides the surrogate shall "make a good faith effort" in analyzing the factors enumerated in the statute. Va. Code Section 54.1-2986(A). The statute further provides that anyone may petition the court to enjoin the withdrawal of medical care "upon finding by a preponderance of the evidence that the action is not lawfully authorized by this article or by other state or federal law." Va. Code Section 54.1-2986(E).

In two 1997 cases, *Washington v. Glucksberg*, 521 U.S. 702, 117 S. Ct. 2258 and *Vacco v. Quill*, 521 U.S. 793, 117 S. Ct. 2293, the U.S. Supreme Court held that state statutes banning assisted suicide are constitutional. In both cases, Chief Justice Rehnquist, citing *Cruzan*, *supra*, emphasized that there was a "distinction between letting a patient die and making that patient die." *Washington*, *supra*, at 715; *Vacco*, *supra*, at 802-803.

Although a constitutionally protected framework exists in most states for the patient's family to elect to withdraw medical care of the incompetent patient, it is still extremely difficult for the family to make such an election. The family members often cannot emotionally accept the futility of the situation even if they intellectually understand it. This may be true even where the family has been previously told by the patient that he or she would want to be allowed to die if in a vegetative condition. The conflict experienced by the family may be immense. There may be disagreement among family members regarding termination of treatment. Many states, such as Virginia, set forth a priority of persons, based upon kinship, who have the authority to make the decision. Nonetheless, as a practical matter, even if the ultimate decision maker wants to terminate treatment,

he or she will often defer to those other family members who do not want to terminate treatment. In one highly publicized case in Virginia, *Gilmore v. Finn*, 259 Va. 448, 527 S.E. 2d 426 (2000), the Governor of Virginia, James Gilmore, actually filed a petition to enjoin the withdrawal of hydration and nutrition to a patient in a vegetative condition where there was disagreement between the patient's wife and guardian and the patient's parents and sibling regarding whether or not the patient should be allowed to die. Ultimately, the court held that while the Governor had the right to intervene in the case in order to seek an "authoritative construction" of Virginia's right to die statute, the patient's wife and guardian indeed had the authority to direct her husband's physicians to withdraw hydration and nutrition for him since she was the first person in priority as enumerated in Virginia Code Section 54.1-2986. *Id.* at 455, 458.

Perhaps the most highly publicized case has been the Terri Schiavo case. As in *Finn*, there was a controversy between the spouse of a vegetative patient who wanted his wife to die and the parents who did not. Ms. Schiavo collapsed in her home in 1990, suffering from heart failure causing a severe anoxic brain injury, which left Ms. Schiavo in a vegetative state. Ms. Schiavo remained in a vegetative state for 15 years. During this time period, the parties litigated the case in the state and federal court system. After Ms. Schiavo's husband prevailed in the Florida courts, the Florida legislature actually passed legislation, authorizing the Governor to issue a one-time stay of withdrawals of life sustaining measures where the patient did not have a written advance directive and a family member had challenged such withdrawal. Immediately after the legislation was enacted, Governor Jeb Bush issued a stay against the withdrawal of nutrition and hydration for Ms. Schiavo. In September, 2004, the Florida Supreme Court ruled that this legislation was unconstitutional. After this ruling, Ms. Schiavo's parents pursued every available judicial and legislative avenue to avoid having Ms. Schiavo's feeding tube removed. In March, 2005, the U.S. Congress passed a law, signed by President Bush, to allow Ms. Schiavo's parents to seek redress in the federal courts to prevent removal of Ms. Schiavo's feeding tube. Subsequent thereto, the parents filed a petition in federal court to enjoin the removal of the feeding tube, which was denied in the U.S. District Court for the Middle District of Florida, the 11th Circuit Court of Appeals, and the U.S. Supreme Court. With no other forums left to seek an injunction of removal of the feeding tube, Ms. Schiavo's tube was removed, and she died on March 31, 2005. The controversy surrounding the case was covered extensively by the media worldwide. As a result of the Terri Schiavo case, the debate regarding a person's right to die has intensified to a level never previously seen. Only time will tell if the debate results in revisions of the states' right to die laws.

In the context of the dilemmas which arise in such cases, the clinician should be honest and direct in conveying diagnostic and prognostic information to the family. If the physician is not comfortable providing such information, then an adequately qualified professional should be consulted. Likewise, the trial attorney, too, should be forthright in his discussions with the family about the legal directives which are in place. At the same time, both the clinician and trial attorney must be sensitive to the family's emotional needs and dynamics. For a discussion of the medical and ethical issues facing a clinician in severe traumatic brain injury cases, see "Medicolegal Aspects of Severe Traumatic Brain Injury", co-authored by Dr. Nathan Zasler and Irvin V. Cantor (10).

### **ANATOMY OF A WORKER'S COMPENSATION TBI CASE**

Worker's compensation is a statutorily created program which exists in each state to compensate workers who get injured in the workplace. Unlike the general tort system, where liability is generally determined by fault, worker's compensation is not a fault-based program, but rather compensates the injured worker so long as the injury arose out of the job while the worker was in the scope of his employment. If an injury is deemed compensable, then the worker is usually entitled to indemnity benefits for his lost wages and medical benefits for any medical expenses incurred as a result of the injury.

Many TBI's arise as a result of workplace accidents. Most of the worker's compensation litigation involving TBI's deals with either: (1) causation, whether or not the injury to the brain was caused by the workplace accident, or (2) the extent of damages, what sequelae are attributable to the TBI. Some states provide for lifetime benefits for workers who suffer TBI's. The central issue in lifetime benefit litigation is whether or not the worker is permanently unable to work as a result of the TBI. For example, Virginia Code Section 65.2-503(C)(3) provides for lifetime awards "when there is injury to the brain which is so severe as to render the employee permanently unemployable in gainful employment."

The worker's compensation case is generally initiated by the filing of a claim by the employee or employer. If the case is not contested, then generally the employer's worker's compensation carrier will voluntarily provide benefits to the worker. In most states, the worker's compensation carrier has the right to designate the treating physician for the injured worker. If the case is contested, then generally the claimant and the employer will be represented by counsel, who will litigate the case in the worker's compensation system.

The worker's compensation system is typically administered outside of the state's general court system,

usually by a Worker's Compensation Commission. Worker's compensation cases are generally heard by an administrative judge or deputy commissioner, and not by juries. Pre-trial discovery is typically allowed in worker's compensation cases, including subpoenas of documents, interrogatories, and depositions. Attendance at the hearing of the case may be compelled by subpoena. Most states provide that the expert witness fees for the professionals who testify in worker's compensation cases must be approved by the Worker's Compensation Commission.

The percentage of TBI worker's compensation cases that are contested is much higher than other types of injuries. This is due primarily to the fact that disagreements between the parties in TBI cases often arise over causation, extent of damages, and whether or not the claimant is permanently unemployable. Consequently, TBI healthcare providers often are called to testify in worker's compensation cases. It is usually a wise idea for the healthcare provider who is asked to testify in a worker's compensation case to clarify at the outset with the attorney requesting his or her testimony what the rules are regarding the format of the testimony and the payment of the fees for testifying.

### **ANATOMY OF A PERSONAL INJURY TBI CASE**

TBI's resulting from motor vehicle collisions, recreational accidents, use of defective products, trips and falls at dangerous premises, and many other sources are the subject of personal injury cases. These cases are litigated in the traditional court system and usually by a jury.

TBI personal injury cases are becoming increasingly prevalent as society and the legal community is being made more aware of the silent epidemic of traumatic brain injuries. The vast majority of TBI litigation in the United States involves mild TBI's. The most contested issues in TBI personal injury cases are the same as in worker's compensation cases, namely causation and extent of damages.

The TBI personal injury case is initiated by the plaintiff filing a lawsuit, usually called a Complaint. The defendant responds to the lawsuit, usually with an Answer. The parties then engage in pre-trial discovery of the lawsuit. Discovery typically consists of interrogatories between the parties, subpoenaed documents from the parties and others, including the treating healthcare providers of the plaintiff, depositions of the parties and others, including the treating healthcare providers of the plaintiff, and independent medical examinations of the plaintiff by healthcare providers selected by the defendant or the court. Discovery is usually a lengthy process, often taking many months and sometimes years.

Discovery in TBI cases is usually more extensive than in other types of injury cases. The defense often

wants to know everything it can about the plaintiff's pre-morbid condition, in order to determine if the plaintiff's problems can be attributed to conditions or events that existed before the incident in question. Additionally, it is not at all uncommon for the defense to request multiple independent medical examinations of the plaintiff, including examinations by a physician and neuropsychologist.

After discovery is completed, the case is scheduled for trial. Trial of a personal injury case typically consists of the following segments: (1) voir dire, where the prospective jurors are questioned by the court and counsel; (2) selection of the jury by counsel; (3) opening statements by counsel; (4) presentation of the plaintiff's case, the plaintiff proceeding first since the plaintiff has the burden of proof; (5) presentation of the defendant's case; (6) presentation of rebuttal evidence by the plaintiff regarding new matters raised by the defendant's case; (7) instructions of the jury by the court; (8) closing argument by counsel; and (9) deliberation by the jury. Trial of a TBI case usually takes longer than trials of other types of injury cases. This is due, in large part, to the fact that the court and the jury must be educated about traumatic brain injury, often resulting in counsel spending more time in talking to the jury, calling more lay and expert witnesses to the stand, and presenting more demonstrative evidence.

### **ANATOMY OF A MEDICAL MALPRACTICE ABI CASE**

Medical malpractice cases involve claims of negligence in providing medical care, brought by a patient or patient's representative against a health care provider. Most states have statutes which define "health care provider" and set forth procedures for bringing and litigating medical negligence claims. Like personal injury cases, medical malpractice cases are generally litigated in the traditional court system and usually decided by a jury.

The plaintiff must prove three basic elements to prevail in a medical malpractice case: (1) the health care provider deviated from the standard of care in his medical treatment; (2) the deviation of the standard of care caused the injury suffered by the plaintiff; and (3) the plaintiff suffered damages as a result of the injury caused by the deviation of the standard of care. Standard of care is generally "that degree of skill and diligence practiced by a reasonably prudent practitioner in the field of practice or specialty" of the defendant. (Va. Code Section 8.01-580.20, which definition is typical of most state statutes in the United States.) In order to prove a breach of the standard of care, it is almost always necessary for the plaintiff to present one or more expert witnesses to testify at trial that the defendant's actions constituted such a breach. It is also usually necessary for the plaintiff to present one or more expert witnesses to testify on the

subject of causation and damages. As a practical matter: (1) it is often quite difficult for plaintiffs to locate good, qualified expert witnesses to give the testimony required to prevail and (2) physicians, nurses, and other health care providers are often well liked and respected in their community and by the juries in their community. Consequently, over 70% of all medical malpractice cases taken to trial in the U.S. result in defense verdicts.

Many states have statutes which provide for certain screening procedures and caps on damages applicable only to medical malpractice cases. Among these statutes are: (1) requirements that a plaintiff have a qualified expert witness provide an opinion that the medical care provided deviated from the standard of care as a condition precedent to filing a lawsuit; (2) requirements that the case be reviewed by a medical malpractice review panel before the case can proceed to trial; (3) requirements that certain allegations of medical negligence (such as birth related injury claims) be brought as administrative proceedings outside of the traditional tort system; and (4) caps on damages, wherein the plaintiff may not recover more than a certain maximum recovery, determined legislatively.

Brain injuries are the subject of many medical malpractice cases. Birth injury cases resulting in either anoxic/hypoxic/ischemic or structural injury to the brain are probably the most prevalent type of acquired brain injury ("ABI") medical malpractice case. Cases involving hypoxic-ischemic brain injuries ("HIBI") caused by alleged negligence in surgery, anesthesia, or other circumstances of intubation or extubation are perhaps the second most prevalent type of ABI medical malpractice case. Other types of ABI medical malpractice cases brought with some frequency include allegations of negligent surgery resulting in structural injury to the brain and failure to diagnose malignant brain tumors and meningiomas.

As a general rule, medical malpractice cases involve a much higher percentage of severe brain injuries than personal injury cases. This is due primarily to the fact that so many of these cases involve anoxic, hypoxic or ischemic injuries resulting in profound sequelae for the patient.

The discovery and trial of a medical malpractice case are generally the same as that for personal injury cases, as set forth in the previous section. ABI medical malpractice trials are usually quite complicated for the jury, for not only does the jury need to understand the medical procedures in question, but also the mechanism of the brain injury. The voir dire questioning of jurors in ABI medical malpractice cases often takes a longer period of time than in other types of negligence cases. There are usually more expert witnesses called to trial in ABI medical malpractice cases than in other types of cases. Also, counsel in ABI medical malpractice cases frequently use demonstrative illustrations, models, and charts to aid the jury on understanding the issues in the case.

## INDEPENDENT MEDICAL EXAMINATIONS

The rules of civil procedure in federal court and in almost all state courts provide that a party in a lawsuit involving the physical or mental condition of a person may request an examination of the person by a physician or health care provider of the party's choosing. Federal Rules of Civil Procedure, Rule 35 (11), which serves as the model for many states' procedures, provides as follows:

### (a) Order For Examination

When the mental or physical condition (including the blood group) of a party or of a person in the custody or under the legal control of a party, is in controversy, the court in which the action is pending may order the party to submit to a physical or mental examination by a suitably licensed or certified examiner or to produce for examination the person in the party's custody or legal control. The order may be made only on motion for good cause shown and upon notice to the person to be examined and to all parties and shall specify the time, place, manner, conditions, and scope of the examination and the person or persons by whom it is to be made.

### (b) Report of Examiner

If requested by the party against whom an order is made under Rule 35(a) or the person examined, the party causing the examination to be made shall deliver to the requesting party a copy of the detailed written report of the examiner setting out the examiner's findings, including results of all tests made, diagnoses and conclusions, together with like reports of all earlier examinations of the same condition. . . .

These examinations are commonly referred to as "independent medical examinations" ("IME's"). The physician or other health care provider who performs such an examination does not have a traditional physician-patient relationship with the examinee. On the contrary, the examiner's role is to serve as an independent resource to provide an unbiased forensic opinion regarding the mental or physical condition of the examinee. The AMA ethics guidelines (12) define the IME physician—patient relationship as follows:

. . . .IME's are responsible for administering an objective medical evaluation but not for monitoring patients' health over time, treating patients, or fulfilling many other duties traditionally held by physicians. Consequently, a limited patient—physician relationship should be considered to exist. IME's still are expected to evaluate objectively patients' health or disability, maintain confidentiality, and disclose potential or perceived conflicts of interest. In addition, upon discovering important health information or abnormalities during the course of the examination, IME's are expected to inform the patient about the condition, ensure that they understand fully the diagnosis, and suggest that they seek care from a qualified physician.

Ideally, even though the examiner is chosen and paid by the party requesting the examination, he or she should resist the temptation to try to please the party who engaged his or her services. The written report prepared by the examiner should be thorough and complete, listing all of the written materials reviewed by the examiner, the results of all of the examinations and/or testing conducted by the examiner, the opinions of the examiner, and the basis for each such opinion.

IME examiners should realize that once they undertake an IME, they will in all likelihood have to give a deposition, usually requested by the examinee's attorney, and if the case does not settle, testify at trial. Sometimes in lieu of testifying at trial, the deposition of the IME examiner, usually taken by audio-visual means, may be used. The deposition which is used as evidence at trial is often referred to as a "de bene esse" deposition. If there is a reason the IME examiner is unable or unwilling to attend trial, he or she should make that known at the outset to the attorney requesting the IME.

In TBI cases especially involving mild TBI's, there is often disagreement between the parties about: (1) whether or not the plaintiff suffered a TBI; (2) the extent of the TBI and the true sequelae resulting from it; and (3) the cause of the deficits and problems suffered by the plaintiff. Consequently, IME's are routinely requested in mild TBI cases. In fact, it is not at all uncommon for the defense in TBI cases to request multiple IME's, including an examination by a physician specializing in neurorehabilitation and a full battery of testing by a neuropsychologist.

A frequently litigated issue in mild TBI cases is what role does the plaintiff's pre-morbid history play versus the traumatic event, such as a motor vehicle collision, as a causative factor in the plaintiff's post-accident functioning. When faced with this issue, the IME examiner should request and review all available pre-morbid records of the plaintiff, including medical, educational and vocational records, and be sure to list in the IME report all of the documents so reviewed. It is wise for the IME examiner to pay close attention to documents dealing with the level of functioning of the plaintiff to determine if there is a discernible difference between the pre-morbid and post-accident performance. In the event the IME examiner is of the opinion that the deficits suffered by the plaintiff are multifactorial in nature, then he or she should set out in detail in the IME report each of those factors and how they have impacted the plaintiff.

In TBI cases there seems to be an unusually high number of experts who are overly dependent financially on medico-legal cases in their practice. These "professional" expert witnesses sometimes derive a very large percentage of their income from certain attorneys or sides in the litigation who hire them. Unfortunately, there are some experts who routinely find in favor of the party that hires them. It is strongly recommended that those experts

who make themselves available for IME's do not compromise their impartiality and objectivity. For a discussion regarding the ethical considerations in IME's following TBI, there are several in-depth articles, co-written by Nathan Zasler, M.D. and Michael Martelli, Ph.D. (13–16).

### EXPERT WITNESS TESTIMONY IN A TBI CASE

As a general rule, only expert witnesses, qualified as such by the court, are permitted to give opinion testimony at trial. Rule 702, Federal Rules of Evidence (17), upon which many state statutes are based, reads as follows:

*Rule 702. Testimony by Experts*

If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

It is not necessary that a person be a practitioner of a science or technical profession in order to qualify as an expert. Rather, the person must have sufficient expertise in his or her field that the expert's opinion will be of benefit to the trier of fact. The court has discretion to qualify the person as an expert in a particular field so long as the person is shown to possess sufficient expertise in the professional field.

An expert's opinion testimony must be based upon reliable facts and assumptions. Testimony which is speculative, based upon faulty assumptions, or is otherwise determined to be "junk science" is inadmissible. In *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), the Supreme Court of the United States, applying Rule 702 of the Federal Rules of Evidence, set forth the following factors for the trial judge, as the "gatekeeper" for the admissibility of such evidence, to determine if the expert's testimony possessed requisite scientific validity:

1. The theories and techniques employed by the scientific expert have been tested;
2. The theories and techniques have been subjected to peer review and publication;
3. The techniques employed by the expert have a known error rate;
4. The techniques employed by the expert are subject to standards governing their application; and

5. The theories and techniques employed by the expert enjoy widespread acceptance.

Using this test, the Supreme Court remanded a birth injury case back to the trial court so that the trial judge could decide if the proffered expert testimony, regarding whether or not the mother's prenatal ingestion of the drug, Bendectin, was shown to cause birth defects, was admissible. Prior to the five-prong test of *Daubert*, the rule was that expert opinion based upon a scientific technique was inadmissible unless the technique is generally accepted as reliable in the relevant scientific community. *Frye v. United States*, 54 App. DC 46, 293F. 1013 (1923). Since 1993, the *Daubert* test has been used by a multitude of trial judges to determine the admissibility of scientific expert testimony. This litigation has resulted in a complicated, often contradictory set of results. A useful website dedicated to the rule espoused in *Daubert* and links to post-*Daubert* cases, articles, tactics and other materials regarding determination of the scientific validity of expert testimony is "Daubert On The Web", [www.daubertontheweb.com](http://www.daubertontheweb.com) (18).

TBI cases, perhaps more than any other type of injury case, typically involve multiple expert witnesses. This is due primarily to the fact that the court and the jury are generally unfamiliar with brain anatomy and function. A sampling of expert witnesses often involved in TBI cases includes neurologists, neurosurgeons, psychiatrists, neuropsychiatrists, neuropsychologists, neuroradiologists, nuclear medicine specialists, speech language therapists, physical therapists, occupational therapists, vocational specialists, life care planners, accident reconstructionists, forensic engineers, and economists.

TBI physicians, as a general rule, have little trouble qualifying as expert witnesses and giving opinion testimony at trial. For example, since it is well established in the medical literature that complete loss of consciousness is not a prerequisite for a diagnosis of TBI, opinion testimony from a TBI physician to that effect is uniformly permitted. However, when the physician bases his or her opinions on assumptions that are controversial and speculative, then such specific opinions may not be allowed. One area of much litigation is the reliance by the physician on abnormal functional imaging studies of the brain to diagnose TBI, discussed in more detail herein on pages 30–31.

Non-physician experts in TBI cases are much more likely to have their testimony excluded as unreliable. Some of the experts in TBI cases whose opinions have been disallowed include accident reconstructionists, who try to determine the speed of crash vehicles by crush analysis, and forensic engineers, who try to determine the amount of force exerted on an occupant of a vehicle in a collision. In most states, neuropsychologists are permitted to give their opinion as to whether or not a person suffered a TBI. However, a recent Virginia case, *John v. Im*, 263 Va. 315, 559 S.E. 2d 694 (2002), held that since the

neuropsychologist was not a medical doctor, he was “not qualified to state an expert medical opinion” regarding the cause of the patient’s brain injury.

Expert witnesses generally bill hourly for the time they spend on medico-legal matters. The party who has hired the expert generally pays the expert’s fees. The opposing party is required to pay the expert for the fees incurred in responding to pre-trial discovery, whether by deposition or interrogatories. Rule 35(b) (4)(c)(i), Federal Rules of Procedure, states that:

(i) the court shall require that the party seeking discovery pay the expert a reasonable fee for time spent in responding to discovery. . . .

A “reasonable fee” generally includes the customary hourly fee the expert charges for medico-legal work. It is strongly suggested that the expert keep detailed, accurate records of his or her time in a case. This is especially true in TBI cases where the expert may have voluminous records to review and longer than usual depositions to give.

Some practical tips for expert witnesses are:

1. Always maintain your impartiality and objectivity.
2. At the outset of a case, clearly communicate with the attorney who has engaged your services about the scope of your role, your availability for litigation, and the financial terms of your engagement.
3. Carefully and thoroughly record your examination results, observations, or other notes in a legible, preferably typewritten, manner.
4. Review all pertinent records and data.
5. Accurately keep and record the time you spend on the case.
6. Always remain courteous and professional with all litigants and their attorneys.
7. Thoroughly review all relevant records and data prior to any deposition or trial.
8. Understand the disparate roles of the participants: your role as the expert is to provide objective scientific or technical opinions, whereas the role of the attorneys and the litigants is to win.

### LAY WITNESS TESTIMONY IN A TBI CASE

While much time and attention is given to the testimony of expert witnesses in TBI litigation, the most important evidence usually is the testimony of the plaintiff and those persons who best know the plaintiff. Invariably, if you ask trial attorneys who regularly handle TBI cases what is the most critical element in a TBI case, they will tell you it is the quality of the plaintiff and his or her lay witnesses. The reason for this seems obvious: the jury, whose job it is to decide if, and how, the plaintiff is affected by the TBI, is most influenced by: (1) how the plaintiff presents at trial

and (2) what those who best know the plaintiff say about how the plaintiff has been affected by the TBI.

Despite this seemingly obvious focus, health care providers and attorneys often fail to consider the reports of those closest to the person who sustained a TBI. This emphasis on opinions by experts, to the exclusion of reports by lay witnesses, not only fails to provide a comprehensive view of the case, but typically results in an unsatisfactory outcome at trial.

Individuals who sustain TBI’s usually do not have good insight about their deficits. This phenomenon is probably due to the nature of the injury, itself, (e.g. frontal lobe dysfunction) or to the fact that the patient is in denial over his or her condition or to a combination of these factors. The most accurate description of the TBI patient typically comes from a spouse, a sibling, a child, a best friend or someone else who best knows the patient.

In diagnosing a TBI and the resulting deficits suffered by the patient, the physician, neuropsychologist, or other health care provider should make an effort to learn the reports of family, friends, co-workers, and others close to the patient about the ways the TBI has affected the patient. It is helpful if the health care provider talks to those who know and regularly interact with the patient. It is also wise for the health care provider to obtain school records, job evaluation reports, or other documents which memorialize the observations of others about the TBI patient. Without consideration of the reports and observations by others of the TBI patient, it is very difficult for the health care providers to accurately determine the pre-morbid and post-traumatic conditions of the patient. Moreover, if the health care provider has not considered the reports of lay witnesses prior to reaching his or her opinions, then the health care provider will be quite vulnerable to attack in cross-examination at deposition or trial.

The trial attorney should make sure to discover and develop lay witness testimony about the TBI patient. Without such testimony, the jury will be left with many unanswered questions and will not be motivated to render a verdict in favor of the party who disregarded such testimony.

Sometimes the inquiry regarding lay witness observations of the TBI patient will result in the discovery that the patient had complained of similar deficits many times before the traumatic event. Other times, the inquiry will result in the discovery that the patient’s life has been completely altered as a result of the TBI. In all cases, proper analysis of the TBI case can only be achieved if due consideration is given to the reports by those who best know the TBI patient-plaintiff.

### DEMONSTRATIVE EVIDENCE IN A TBI CASE

Individuals who suffer TBI’s frequently appear perfectly fine. They often do not have any disfigurement, no scars,



no limp, and no visible sign of impairment. It is no wonder TBI victims are referred to as “the walking wounded.” Consequently, in the trial of TBI cases, there is much use of visual aids to assist the jury to understand the TBI and its sequelae. This type of evidence is commonly referred to as “demonstrative evidence” because it is used to demonstrate and clarify testimony. There is perhaps no other type of injury case which necessitates the use of demonstrative evidence more than the trial of a TBI.

Since the TBI was caused by a traumatic event, evidence to explain how the forces of the accident were exerted on the plaintiff’s head and brain are often used. In motor vehicle collisions, photographs of the vehicle are almost always introduced into evidence. Such photographs may include not only the body damage to the vehicles, but also a bent steering wheel, a broken headrest or seat, or a shattered windshield. In many cases, photographs of the interior and exterior of a windshield, which has a spider web pattern as a result of contact with the plaintiff’s head, are introduced into evidence.

A simple but powerful way to demonstrate an acceleration/deceleration injury to the brain is for the physician to use a model of the skull and brain in his or her testimony. While using the model, the physician can explain that the skull is a rigid structure, but the brain has the consistency of jelled gelatin, and that rapid changes in direction of movement of the skull and brain can cause stretching and shearing of tissue and fibers to the brain. There are some interesting short animated films available to depict this process. Two such films are: (1) “Closed Head Injury”, produced by Technical Medical Animation Corporation, Denver, Colorado (19) and (2) “Understanding Mild Traumatic Brain Injury”, produced by Body Mind Publications, Olympia, Washington (20). Another excellent source for video animations of types of TBI, brain functioning and mechanics of TBI is the Traumatic Brain Injury Resources Guide website, [www.neuroskills.com](http://www.neuroskills.com) (21).

Structural imaging tests of the brain, x-rays, CT Scans, and MRI’s, are routinely used in TBI trials, especially where the plaintiff has suffered a skull fracture, an intracranial or extracranial bleed, or other discernible brain lesion. Sometimes it is helpful to construct 3-D models from the CT and MRI computer tapes since these 3-D models can show shape, form and color for the jury.

Functional imaging studies, testing brain activity, are also used quite often in TBI cases. This is due in large part to the fact that structural imaging studies of persons sustaining mild TBI’s generally are negative. The most often used studies are PET Scans (Positron Emission Tomography), SPECT Scans (Single Photon Emission Computerized Tomography), EEG (Electroencephalography) and QEEG studies (Quantitative Electroencephalography).

Abnormalities in brain function are not diagnostic of brain injury in and of themselves. Many clinical conditions can produce abnormalities on PET and SPECT. Consequently, caution must be exercised when using abnormal functional imaging studies in TBI litigation. The use of such tests at trial depends upon several factors: (1) the type of equipment used in the test procedures; (2) the credentials, expertise and experience of the technician conducting the test procedures; (3) the credentials, expertise and experience of the clinician interpreting the test results; and (4) the manner in which the test results are used in the clinician’s analysis. The admissibility of functional imaging tests of the brain have been the subject of much litigation throughout the country, where the focus of the courts has been on whether or not the test results are “reliable scientific evidence”. The overwhelming majority of these cases hold that the results of functional imaging tests are admissible at trial for a qualified expert to use as a factor (as opposed to “the sole factor”) in arriving at his or her opinion about the TBI. Consequently, when an expert intends to use a functional imaging test in his or her testimony, it is strongly recommended that the expert make it clear that the results of the functional imaging test are being used as a confirmatory factor in his or her opinion about the TBI and the resulting brain function. When a PET or SPECT Scan is used at trial, as with CT’s and MRI’s, it is often helpful to have 3-D models made from the computer tape of the PET or SPECT.

Most TBI trials include testimony from neuropsychologists who have performed neuropsychological evaluations of the plaintiff. Often the plaintiff has undergone multiple neuropsychological evaluations prior to trial. Many times these serial evaluations will result in clear patterns of test performance. When a clear pattern is demonstrated, sometimes graphs and charts depicting test performance are used to help the jury understand the person’s deficits or lack thereof. Such visual aides of neuropsychological test results should be used only when such results are significant, correlate with the clinical examinations of the person, and are otherwise not subject to attack on cross-examination.

There are a myriad of other types of demonstrative evidence commonly used in TBI cases. Some of these are: (1) illustrations of the brain and its network of neurons; (2) “day in the life” videos of the plaintiff, depicting some of the problems the plaintiff experiences on a daily basis; (3) surveillance videos, surreptitiously taken by the defense, to show the plaintiff actually engages in activities inconsistent with his or her claimed deficits; and (4) blow-ups of academic records and job evaluations.

A knowledge of the use of demonstrative evidence in TBI cases is helpful for the clinician or expert witness involved in a TBI case to interact with counsel or the injured plaintiff.

## PROTECTION AND PRESERVATION OF THE TBI CLIENT'S RECOVERY AFTER SETTLEMENT, VERDICT OR AWARD

The TBI case is not over just because the plaintiff has achieved a settlement or verdict. Rather, attention must be given to how the monetary proceeds achieved in litigation should be received and structured. Failure to properly structure these funds is a trap for the unwary and may result in the loss of benefits otherwise available to the injured person.

Individuals who sustain a TBI are often eligible for Social Security, Medicare, and Medicaid benefits. Social Security and Medicare benefits are generally available to the person (or his relative) who has made the requisite payments of FICA taxes to the federal government. These benefits provide monthly income and medical coverage. If the person does not qualify for Medicare, he or she still may be eligible for Supplemental Security Income (SSI) and Medicaid benefits. SSI provides monthly income benefits and Medicaid provides medical benefits. SSI and Medicaid are "needs based" programs, insofar as the individual must meet an asset-based test in order to qualify. In addition to monthly income and medical benefits, SSI and Medicaid recipients are also eligible for long-term care and various rehabilitation programs. For the TBI victim facing substantial long-term care expenses, SSI and Medicaid benefits are a vital resource.

The creation of a properly drafted trust to hold the funds recovered by the plaintiff in a TBI case can serve to protect the plaintiff's eligibility for needs based programs. Assets held in these trusts, often referred to as "Special Needs Trusts" or "Settlement Trusts", are not considered available to the beneficiary because title to the assets does not vest in the beneficiary until and unless the trust is terminated. The beneficiary of such a trust, having retained his or her eligibility for needs based benefits, continues to receive SSI and Medicaid benefits, and uses the funds held in trust to pay for needs not covered by SSI and Medicaid, hence the name "Special Needs Trust."

Special Needs/Settlement Trusts not only preserve the beneficiary's eligibility for needs based benefits, but typically also provide for professional investment management of the trust funds, a function many TBI victims are unable to properly perform. The trust must be created by a court. The court's jurisdiction is based upon the incapacity of the beneficiary to reasonably understand and/or manage the proper disbursement of the TBI case proceeds.

The constantly evolving laws regarding trusts and federal and state benefits are quite complex. Consequently, it is generally wise for a competent trust attorney to draft the Special Needs/Settlement Trust. A complete understanding and working knowledge of these laws is usually not within the province of the plaintiff's trial attorney.

The proper use of a Special Needs/Settlement Trust can maximize the funds and benefits available to the TBI victim. This can often result in a dramatic enhancement of the life of the person who has sustained a TBI.

## CONCLUSION

The epidemic of TBI in our society has spawned an ever-increasing myriad of legal issues. These issues are vast and complex. Hopefully, this chapter has shed some light on some of the pertinent medico-legal aspects of TBI.

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# 63

## Ethical Issues in Clinicolegal Practice

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### INTRODUCTION

The general requirement for ensuring ethical conduct in any form of clinicolegal evaluation is rendered even more imperative when confronted by the complex, often subtle range of effects and severities of impairments of the traumatized brain. The clinicolegal evaluator must be especially cognizant of rules and guidelines for assigning causation for singular etiologies, or relative attribution for multifactorial circumstances; of the pathomechanics of various traumatic scenarios; of the differential diagnosis of psychological versus neurological disorders; and of the interplay of emotional states and needs with psychological functions and cognition.

Pronouncements on the severity or even existence of any impairment must be rigorously supported by objective evidence and strictly limited to reasonable inference.

If *'the past is often prologue'* then it becomes critically important to establish an accurate, complete prior history of all injuries or illnesses capable of affecting the brain. It is equally critical to clarify all potentially relevant comorbidities, especially social/situational distress, sleep deficit, pain, OTC and prescription medication 'side' effects, and surreptitious substance use/abuse.

The evaluator must be fully aware of active controversies concerning the therapeutic efficacy of various interventions, for both minor and severe brain injury: while long, expensive programs of care can lead in some

cases to profound improvements in insight, impairment control and quality of life, in other cases the result may be financially profligate, devoid of discernible benefit, or even tainted by serious iatrogenic harm.

Setting the bar high, creating specific, rigorous criteria for ethical and competent evaluation and testimony, with suitable tests and benchmarks, appears to be the trend in the courts (1), wherein clinicolegal expertise is most needed. It behooves each clinician to know where the risks lie, and to avoid falling into practice patterns of substandard work, or permitting exposure to real or even apparent ethical misconduct. A key risk area concerns lack of familiarity with relevant, and especially with recent important developments including: court rulings; new diagnostic procedures and measures of functional capacity; improved validity and reliability data for currently used clinical tests and outcome measures; and changes in relevant ethics codes (e.g. the 1999 AMA Ethics Guidelines on Physician/Patient Relationships in the Context of Independent Medical Evaluation, and the 2003 NAN position paper on independent and court-order forensic neuropsychological examinations (2–4).

Similarly, it is appropriate to expect health care professionals to take a proactive role in individual professional as well as general quality assurance. When lack of competence, apparent or actual ethical misconduct is observed in one's colleagues, the evaluator is obligated to take appropriate steps to defend the consumers of our

services and thereby safeguard the public's trust in the healing professions in general and in independent expert evaluation in particular.

Ongoing education is required at all levels, from student to practitioner to academic, on the application of ethical principles to clinicolegal practice, in order to create and sustain ethical professional behavior in ourselves and in our colleagues; and as a legacy for the generation of evaluators who will surely follow us.

## SPECIAL ETHICAL CHALLENGES OF THE ADVERSARIAL ENVIRONMENT

### The Practice Paradigm Shift

The adversarial clinicolegal environment contrasts sharply with that in which health caregivers train and work. Within the health care environment the emphasis is on selfless aspects of professionalism including personal sacrifice, devotion to duty and to public health; with the primacy of the fiduciary 'duty of care' reflected in patient advocacy. These principles shape the attitude of each healthcare professional when assessing and treating in his/her clinical practice.

However, the clinicolegal environment is typically dominated by adversarial polarization. The person, already having (inadvertently) assumed a *sick role* by being rendered a *patient* through loss of health secondary to injury or illness, acquires (by having taken legal action) some of the typical characteristics of certain sociolegalistic identities or roles: with labels such as *Client*, *Litigant*, *Victim*, *Claimant*, *Disabled Person* and/or *Evaluee*.

Advocacy, by parties supporting or opposing the litigation, tends to be a common basis of request for services, including professional evaluation, caregiving reports, and court testimony. Infrequently, the request may be 'neutral', an invitation for a substantive review expressly for the objective education of the triers of fact. Thus, for many clinicians, upon accepting a request for expert examination of a litigant, the transition from the classroom or treatment clinic to the evaluation setting or courtroom will require a substantial and abrupt perceptual paradigm shift from fiduciary duty to forensic functions; and a corresponding, often ill-informed struggle with novel, sometimes subtle ethical, moral, and legal issues.

As with any anticipated paradigm shift, preventative measures are preferable to remedial actions. Effective professional education can create a heightened appreciation of and corresponding sensitivity to the pitfalls that may be created when conflicting interests encroach upon the clinician who is suddenly challenged to apply general guidelines of routine practice ethics in unfamiliar clinicolegal circumstances.

Unfortunately, many, if not most, clinicians who evaluate and/or treat persons with traumatic brain injury,

as well as those serving on panels that establish policy involving training and certification of professional competency, would acknowledge having had insufficient education/training in the prevalence and nature of special ethical challenges and ethical guidelines specific to the clinicolegal setting.

### Prevalence of Ethical Challenges

The results of a 1992 survey of the membership of the American Psychological Association (APA) regarding ethical concerns in clinical psychology (5) are generally applicable to all evaluating clinicians. Critical incidents were separated into 23 categories of ethical dilemmas. Issues involving forensic psychology ranked fifth, due to concerns about the presentation of false testimony, the attorney's role in eliciting desirable (but possibly false) testimony, the rendering of conclusions that are not grounded in objective data or scientific principles, and the potential for unintentional harm that could result from reporting inaccurate data.

Specifically pertinent to TBI casework is a survey of the membership of the National Academy of Neuropsychology (NAN) which revealed that the majority of the respondents were concerned about examiner competence (64%), inappropriate use of tests (61%), and conflict between the law and ethics (55%) (6).

### Adapting General Biomedical Ethics to TBI Casework

Building upon the universal commitment of the clinician to his/her patient, four core bioethical Principles have been described: *Autonomy*, *Non-Maleficence*, *Beneficence*, and *Justice* (7).

*Autonomy* refers to self-determination; that is, the ability to make healthcare-related decisions independently.

*Non-Maleficence* is closely related to the Oath of Hippocrates, loosely translated from Greek into Latin as: *primum non nocere* (First, Do No Harm!).

The concept of *Beneficence* is more proactive, requiring that there is a promotion of that which is in the best interest of the patient.

In healthcare, the concept of *Justice* typically concerns the equitable distribution of the burdens and benefits of care.

Common to these four Principles is the expectation of a fundamental obligation to respect the patient at all times. Certainly, the fundamental obligation of respect applies equally to when the interaction is solely one of evaluator-examinee, with no clinician-patient relationship. Clinicians are expected to provide equal measures of respect to a person, whether seen in the context of patient or that of evaluee, including courtesy, dignity and

fairness; and spending adequate time during the assessment process.

While the concepts of non-maleficence, beneficence and justice remain closely tied to the universal commitment of respect for the person, there is a need for adaptation to the special circumstances of the medico-legal context, in which the person's goals are those of a litigant, potentially unrelated to his/her concurrent goals as a patient. Although an examiner must recognize and respect the responsibility to bring no direct harm to the examinee during the examination, certain forms of examinations may need to be provocative in order to evoke and test symptoms and signs, including pain, or emotional distress. Thus, the psychiatric interview or neuropsychological testing may result in temporary frustration from challenging cognitive tasks, or in changes in mood due to emotionally sensitive query.

Moreover, although potentially true (tangentially) of the treating clinician examination, findings from a clinicolegal evaluation may have the potential of significantly and directly impacting upon the examinee's diagnostic label, future financial status, treatment or vocational options, environmental modifications, and/or even level of credibility. The successful reconciliation of these three Principles to the clinicolegal environment rests with the appreciation that the duty is owed – as it is with the judiciary – equally impartially to all litigating parties. It is the evaluator's task to conduct the evaluation in a fair manner and to present the results objectively, fully and dispassionately. The court or other party requesting the examination will then have the responsibility to see that the outcome is just. Outcome must never be a factor in the presentation of findings, conclusions or opinions by a clinicolegal evaluator.

An examinee who is denied services or monies based in full or in part on the results of an independent examination may believe that he/she was not treated justly and that the examination did indeed cause harm. However, the evaluator who has treated that individual respectfully and with dignity and has facilitated a meaningful interview, (including listening carefully and reasonably patiently to the examinee's expressed concerns), and then spent sufficient time in examination and in report preparation, will be less likely to be perceived as unfair or acting with maleficence.

With independent examinations, the principle of beneficence does not apply directly to the examinee. The examiner's role is an impartial one, favouring neither the examinee nor the opposing party. Unlike caregiving situations, promotion of the examinee's well-being is not a primary goal. Instead, the examiner's evaluation is conducted to inform the referring party and by extension is for the benefit of the trier of fact or other decision-making body to whom the parties turn for dispute resolution. The examinee, like the other parties to a clinico-legal dispute,

may benefit in whole or in part, or may not benefit at all, from the results of the evaluation and any decisions based upon the results. The examiner has no responsibility to the examinee, and to his/her needs or wishes, beyond courtesy, expertise, thoroughness and objectivity, and must take no interest in the process or outcome, of settlement negotiations or judicial determinations.

As a corollary, the ethical examiner must not be drawn into making partial decisions on the basis of 'universal' axioms such as: '*benefit of the doubt always goes to the patient*'. That axiom certainly belongs within 'when in doubt' decision algorithms relating to patient safety, such as the management of acute chest pain complaints. It does not necessarily apply equally to circumstances where parties have opposing interests in causation or settlements, and have a right to expect an evaluator to function without any decision bias. An inherent, consistent preference for one position or party, no matter how beneficent in intent, not only projects the appearance of bias but may in fact cross the ethical boundary of neutrality, as well as, reduce the utility of the evaluator's conclusions.

There is another aspect to beneficence, related to the clinician's universal societal-legal obligations, from which there is no exemption created within a clinicolegal context. A physician who discovers a clinical condition that could be harmful to the individual or to others has a direct obligation to report that condition to the appropriate body: in the case of unsafe driving (in some jurisdictions), to a driver's licensing authority (e.g. impaired vision / cognition, or seizures); in the case of child neglect/abuse to a children's aide agency. Typically, where mandatory reporting exists, special protocols are created by the authority / agency to safeguard anonymity, in addition to legislation to protect the reporting clinician from lawsuit. Typically the attending clinician or clinicolegal evaluator has no concurrent obligation to the evaluatee, to disclose the fact of reporting.

## AVOIDING ETHICAL MISCONDUCT

### Proactivity

Clinicians, whether they are placed in or place themselves in clinicolegal situations, must make themselves aware of potential ethical pitfalls and must actively take steps to avoid them. Passive reliance on a sincere belief, that by performing competent work one is *a priori* assured of being perceived as 'ethical', is not sufficient protection in the face of the complex and wide range of potential ethical dilemmas, and will not necessarily safeguard against a perception of boundary-crossing leading to an accusation of ethical misconduct. The clinician must instead be assertive in seeking out knowledge, skills, and feedback related to ethical practice; constantly vigilant for evolving dilemmas; and briskly proactive in avoiding or remediating same.

### **Developing and Maintaining Reliable Expert Qualifications**

It is axiomatic that one's qualifications and expertise must be consistent with or exceed currently accepted professional guidelines. Clinicians should strive to maintain high standards of competence in their work, including recognition of and deference to the boundaries of their competencies and the limitations of their expertise, and to provide only those services and use only those techniques for which they are qualified by education, training, or experience.

While variability in education, training, and experience remain, the achievement of eligibility for Board certification (e.g. diplomate or fellowship status) is an accepted basic standard for clinical specialist expertise. This standard is superseded only by acquisition of formal Board specialty or subspecialty certification, which is conferred only through successful completion of a rigorous examination process.

In general, the attainment of Board specialty or subspecialty certification provides the clearest single universal evidence of competence in the relevant area of specialty. Given that Board eligibility is a widely recognized basic standard for expert witness qualifications, it is recommended that clinicians not opting for Board certification should have their credentials independently evaluated by appropriate bodies to verify meeting Board eligibility threshold requirements.

Many organizations offer 'Board certification'. The criteria for attainment of these "Board certifications" vary from merely paying a fee, through varying levels of training, practical experience, written and oral examination. Prior to expending time, effort and funds towards such certification, it is important for the clinician to carefully investigate the organization as well as its certification's inclusionary and exclusionary criteria, including both the stringency of the eligibility requirements and the thoroughness and applicability of the examination processes. Affiliation with an organization which offers certification examination to virtually any applicant, notwithstanding possession of a suitable professional background, or whose certification examination has a 100% pass rate, offers no real validation to one's knowledgeable peers or to a critical court system.

It can be recommended that clinicians involved with clinicolegal evaluation of persons with complex conditions such as TBI: (a) seek rigorous peer review to ensure competence in the general area of assessment, as well as, any special areas of interest, and obtain supervision and documentation that any identified deficiencies have been remediated, (b) obtain Board certification as the most rigorous mechanism of peer review, and (c) exercise care to practice only within the boundaries of competence, and seek consultation from other experts when appropriate.

Continuing education is critical for maintaining expertise. Given the rapidly evolving field of TBI and of brain function research in general, clinicians must maintain a reasonable level of awareness of current general scientific theory and applied practice knowledge. This should include awareness of general trends in the relevant literature, the state of current knowledge, and the significant limitations in said knowledge. Documented, regular attendance at specialty-focused professional conferences and seminars formally signals a significant investment in furthering one's knowledge.

Additional professional activities may demonstrate expertise in specific areas of knowledge or skill. Publications, lectures or seminars given, academic appointments, and administrative positions may all reflect high levels of expertise. However, as with board certification, the manner in which these credentials are obtained can vary considerably. Publications in peer-reviewed media with stringent acceptance criteria represent the highest standard of publication.

Professionals making presentations at national or international conferences are often regarded as accepted authorities in their field, as inferred from the fact of invitation from highly credentialed and merit-discriminating peer conference organizers, particularly those who have a broad spectrum of choice of experts. Faculty or administrative appointments should be evaluated on the manner in which they are earned and the degree of selectivity of the process.

### **Neutrality and Sphere of Expertise**

The American Medical Association's (AMA) Council on Ethical and Judicial Affairs publishes a Code of Medical Ethics (8). The AMA Ethics Code is fairly general; however, it does state that medical experts should "have recent and substantive experience in the area in which they testify and should limit testimony to their sphere of medical expertise." The code further stipulates that the "medical witness must not become an advocate or partisan in the legal proceeding." It further suggests that the medical witness inform attorneys of "all favorable and unfavorable information developed by the physician's evaluation of the case." The latter is of course a universal criterion. Failure to make full disclosure has the appearance of deliberate selectivity, from which flows the inevitable inference of an unbalanced, partial evaluation.

The lay-person is at a significant disadvantage with respect to appreciating the subtleties of the various subspecialty scopes of practice, and the significance of 'positive' (what was found that should not be there) and 'negative' (what should have been there and was not found) findings. Thus, in the assessment of apparent hysterical blindness after a head injury, appreciation of the distinction

between the abilities of a general ophthalmologist and a neuro-ophthalmologist, or between a general psychiatrist and a neuro-psychiatrist, may be critical to appreciating the relative value of various ‘expert’ findings of normality or abnormality. Moreover, a notation that a patient with TBI could not read a sample text is of little value in the absence of clarification of the potential modifying conditions such as prior literacy; or the confirmation that the eyes did not suffer from corneal opacity or medication-induced loss of acuity, uncorrected/poorly corrected vision or poor fitting contact lenses or retinopathies; or that there were no cranial nerve palsies creating diplopia, etc.

### Material Contribution to Case Resolution

The American Academy of Physical Medicine and Rehabilitation (9) published a ‘white paper’ with recommendations for expert witness testimony. This document indicates that the expert witness should serve to educate the court as a whole, rather than representing one side or the other, notwithstanding that the expert may have been retained by one party. The document suggests that the ultimate test for accuracy and impartiality is a willingness to prepare reports or offer testimony that could be presented without alteration for use by either the plaintiff or the defendant. As a corollary, judges have remarked that the ability to accurately discern the identity of the requesting party, merely from reading reports or reviewing transcripts of testimony, potentially signals a lack of genuine neutrality on the part of the evaluator. Three additional recommendations are emphasized: (a) the physician should identify opinions which are personal and not necessarily held by other physicians, (b) a distinction should be made between medical malpractice and medical maloccurrence when analyzing case evidence, and (c) there should be a willingness to submit transcripts of depositions and/or courtroom testimony for peer review.

The American Academy of Neurology and the American Board of Medical Specialties have presented the following guidelines for the physician expert witness: (a) the physician expert witness should be fully trained in a specialty or a diplomate of a specialty board recognized by the American Board of Medical Specialties, and qualified by experience or demonstrated competence in the subject of the case; the specialty of the physician should be appropriate to the subject matter in the case, and (b) the physician expert witness should be familiar with the clinical practice of the specialty for the subject matter of the case at the time of the occurrence, and should be actively involved in the clinical practice of the specialty for the subject matter of the case for three of the previous five years at the time of the testimony. Similar guidelines have also been published by the American Academy of Psychiatry and the Law (10).

### Avoidance of Relational Conflict Issues

The ethical guidelines governing the relationship between an examiner and an evaluatee are special adaptations of universal clinical practice ‘caregiver’ guidelines in which the primary concern is for the safety and welfare of the patient. The caregiver role is ‘active’, involving a ‘fiduciary’ ‘duty of care’ with a predominant focus on *individual outcome*.

In clinical practice, given the perceived power differential between doctor and patient, entering into any personal, scientific, financial, or other relationships with a caregiver has the potential of being exploitative to the patient. Clinical training emphasizes the need for avoidance of excessively intimate personal relationships with a current patient (and sometimes even a former patient).

Building on the Hippocratic Oath, the AMA explicitly expresses the concerns of the profession towards any blurring of the boundaries between the personal and professional relationships of the physician, where boundary violations “may exploit the vulnerability of the patient” or “may obscure the physician’s objective judgment concerning the patient’s health care”. The AMA formalizes its proscription against exploitation of any former patient by declaring any post-caregiving relationship unethical: “if the physician uses or exploits trust, knowledge, emotions or influence derived from the previous professional relationship” and: “At a minimum, a physician’s ethical duties include terminating the physician-patient relationship before initiating a dating, romantic or sexual relationship”.

In direct contrast, the role of the clinicolegal evaluator is ‘passive’ in relationship to the evaluatee and his/her family. The evaluator neither seeks nor accepts any duty of care, and must also firmly and unambiguously discourage any expectation of care. The value of clinicolegal work lies not only in the examiner’s clinical expertise, but equally in impartiality and objectivity, and the extent to which critical powers are applied to case evidence and scientific knowledge – making a material contribution to case resolution.

The guidelines for clinicolegal practice should be adhered to as rigorously as those applicable to the most worrisome of clinical practice circumstances. To ensure that neither real nor apparent conflict of interest enters into the clinico-legal evaluation, an examiner must decline any evaluation involving an evaluatee with whom the examiner has, or has had, a personal, social or therapeutic relationship. The examiner should also decline any evaluation involving an evaluatee who has a personal relationship with any member of the examiner’s immediate family. In essence, safeguarding the perception of neutrality requires that an examiner decline any evaluation circumstance in which he/she can not be entirely free of pressure in regard to presenting candid, complete opinions on issues such as causation, entitlement to benefits, disability, or prognosis; or circumstances in which an observer could develop a reasonable concern.



Clearly, for the clinicolegal examiner, ethical guidelines for encounters and relationships are simple and unequivocal. Aside from the provision of urgent therapeutic services, there must be absolutely no advice or caregiving during the encounter, and no contact or relationship of any kind in the future with an evaluatee or his/her immediate family, until at least the formal conclusion of all clinicolegal proceedings. Clearly, violation of such boundaries carries considerable risk of appearance, if not actual, conflicts of interest. Otherwise, the evaluator could be placed in a position of considerable power and potential exploitation; ironically, the reverse could also be true since the evaluatee or family member might attain a position of considerable influence over the evaluator.

This raises the question of associated or prior relationships. Concerning the former, it is readily evident that the evaluator should avoid any case in which subtle influence might be exerted on him/her, such as when the evaluatee or immediate family is somehow connected through employment, friendship, social or professional group, acquaintance or family relationships. For example, given the likelihood of social encounters it might be prudent to avoid evaluating the parent of a child who is in the same school class as one's own child.

For the purposes of clinicolegal evaluation, any pre-existing relationship that was more than a casual acquaintanceship creates the potential for real or apparent conflict of interest (11). As a general rule therefore, any relationship that may be seen by others, as well as by the parties involved, as having the potential to bias the opinion of the examiner should eliminate that professional from consideration as an examiner (12). However, exceptions may be required, particularly when no other expert in a particular field is readily available and where entitlement to benefit issues requires urgent evaluation. Prioritizing provision of a needed service may outweigh many potential objections. When any such exception is required, the nature of any pre-existing relationship and its potential ramifications on the results of the clinicolegal examination must be disclosed to all parties prior to conducting the examination and should be clearly documented in the subsequent written clinicolegal report. In addition, all safeguards that will be employed to ensure objectivity should be described. As a final corollary, should circumstances change outside of the control of the examiner, as might happen during the course of a clinicolegal case that lasts many years, such that the examiner no longer feels that neutrality and freedom from influence exists, the examiner should notify all parties and offer to withdraw from the case.

### Professional Role Distinctions

The ethical codes discussed to this point emphasize prescription of creation of dual relationships in which the

examiner had/has both a professional and a nonprofessional relationship with an evaluatee. Avoiding conflicts between differing professional roles is of equal importance given the potential for undermining the professional's objectivity and credibility, negatively affecting the parties served.

Equally applicable to physicians and other professionals, Blau (13, 14), identified three different and conflicting professional roles for professionals working in clinicolegal settings: Treating Doctor, Expert Witness, and Trial Consultant.

The *Treating Doctor* is in an active role, with a duty of care. The clinician tends to seek or accept an empathic bond with the patient, and is expected to advocate for the patient in ways intended to improve mental or physical health, or facilitate stable, supportive circumstances. When offering testimony, the Treating Doctor is a special type of fact witness, relying on expertise in helping the triers of fact while describing the symptoms and signs, the investigations done, the treatments provided, and the course and impact of the condition. As a fact witness, the Treating Doctor's reports and testimony must be anchored in his/her findings, diagnoses and treatment records. However, the Treating Doctor is also capable of service as an expert resource to the court, subject to qualifications being reviewed and a determination made as to the limits of testimony for each individual professional. Unlike the lay person, who as a fact witness cannot offer expert opinion but rather can only describe what was personally seen or heard, clinical professionals may be permitted to offer the court more general information about differential diagnosis, natural history of diseases, investigations, treatment paradigms, and prognosis, drawing on professional training and experience. It is of course understood by all parties that any such testimony may be potentially influenced by the underlying treating relationship, but it is expected that when so requested, the clinician will strive to assist the court with full disclosure and cooperation, careful consideration of responses, and avoidance of argumentativeness or disproportionate, impassioned advocacy. The triers of fact will later assign appropriate weight to the testimony. It is never appropriate for a Treating Doctor to enter into contractual arrangements for fee-for-service evaluations of a current or former patient on any basis other than that of the physician-patient relationship.

The *Expert Witness*, having no prior direct knowledge of the examinee, is obligated to obtain special and often exceptionally complete information in order to render an expert opinion. In order to facilitate objectivity, no emotional or other bond can exist with the examinee. All clinical evidence must be evenhandedly reviewed with an approach founded in critical appraisal. It is appropriate to approach the case from a perspective of reasonable skepticism, testing all evidence for reliability and applicability.

The *Trial Consultant* is retained to assist with the critical scrutiny of expert opinions. Given the realities of the adversarial process, the trial consultant may be expected to identify experts on the opposing side who are potentially susceptible to impeachment and to then lay the groundwork for that effort. Clearly, an objective and dispassionate status towards the evaluatee, and towards all other professionals involved in the case, is essential to trial consultancy, in order to offer sound, unemotional advice to retaining counsel.

A further role existing in some circumstances is that of *Case Reviewer*, retained to review the case evidence without direct assessment (evidentiary review), and/or to critically evaluate the assessing evaluators and treating clinicians (peer review). Not all clinicians are comfortable with performing an evidentiary review solely confined to documentation, and leading to expert opinions about a claimant that one has not interviewed and examined. The peer review involves at least the potential of having to state findings critical of one's colleagues' knowledge, clinical acumen, ethics or practices. The Case Reviewer must always declare at the outset of the report precisely what information (such as specific documentation) was relied upon, and that the opportunity for a direct evaluation was not provided. It is appropriate to state whether a direct evaluation might alter the opinion being presented. It is necessary to state whether the documentation was found to be clear and complete, and to indicate the limits of scope and certainty of the opinions that could be derived. For example, a Reviewer might be asked to determine the total percent Impairment of the Whole Person by applying documented clinical findings to the AMA Guides to the Evaluation of Permanent Impairment (15). While the Reviewer is able to offer expert analysis of the proper Chapters, Tables and Figures and Combined Values, the opinion remains entirely dependent on other clinicians' work for the comprehensiveness of the list of diagnoses and impairments and the reliability of the clinical findings. Oftentimes, in the context of a review, incomplete records are provided to the clinician – yet opinions are requested based on the information available. It can be argued that any ethical clinician should never provide opinions without first requesting an opportunity to review all relevant materials. Lastly, given that there is, by definition, no opportunity availed to the clinician to directly examine the injured party in the context of a review, clinicians must be careful, on ethical clinicolegal grounds, regarding opining as to specific impairment and disability related issues.

In general these four roles are separate and distinct and represent differing interests and obligations. Failure to clarify the limits of one's role for both oneself and the other parties involved may lead to inappropriate mixing of roles, with a resultant loss of objectivity and professional accuracy. Notwithstanding which role the clinician is asked to assume, any fixed-outcome oriented solicitation should be

promptly and firmly responded to in unequivocal terms, with clear instruction to the requesting party concerning the ethical limits which govern the professional's participation. Similarly, the professional should decline any request in which remuneration is made contingent on 'satisfactory' outcome (as defined by an interested party) or in which the final fee paid may differ according to settlement terms.

For the Treating Doctor, role conflicts may be further avoided by providing the patient's treatment record instead of a report or testimony (16).

Any role conflicts that do nevertheless arise should be acknowledged in reports and in testimony.

### Immunity of Clinicolegal Work and Expert Testimony

Illustrative of the special role of the Expert Witness is an Ontario court ruling which arose from a class action law suit for damages by several plaintiffs against two clinicians whose clinicolegal evaluations were in compliance with dispute resolution requirements of Ontario's no-fault auto insurance legislation. In dismissing the lawsuit the judge reviewed prior court decisions on point and concluded that the *only* relationship between the plaintiffs and their evaluators involved the assessment of and report on each of the plaintiffs by one or both of the defendants. The legislated dispute resolution process required the defendants to intervene as evaluators, which they did. The ruling set out that clinicolegal evaluators cannot be sued for carrying out their statutory duty because they owe no duty of care to the plaintiffs. They cannot be sued for malpractice because their contact with the plaintiffs was not sufficient to create a medical duty of care to the plaintiffs. They cannot be sued for breach of fiduciary duty because the assessment relationship lacks the element of expectation that the assessor will act in the interests of the plaintiff and so does not give rise to a fiduciary duty in favor of the plaintiffs, and such a duty would be inconsistent with their neutral position. Lastly, they cannot be sued for what they say in their reports because such reports are absolutely protected by witness immunity.

We would note, however, that not all judicial systems act as logically as the Ontario Courts, and one of the authors (Zasler) has personal knowledge of several claims that have come out of clinicolegal expert testimony involvement where experts were sued for, among other things, claims of slander consequential to claiming that someone was symptom magnifying or malingering. Another author (Ameis) has had personal experience with cases in which regulatory bodies have held formal reviews of clinicians in response to complainants objecting to medicolegal reports containing similarly 'provocative' terms. Clinicians should not assume, therefore, that they are totally immune for their actions in the capacity as an expert witness.

There are ways to protect oneself from the effects of such claims, such as by carrying additional insurance (most malpractice policies do not cover clinicolegal work).

Medical Boards and professional peers may also take various actions against unethical clinicolegal conduct when observed with fellow professionals although all too often such conduct is left to fester and propagate as professionals would rather “not get involved” due to potential personal and political ramifications.

## ETHICAL CLINICAL OFFICE PRACTICES

### Use of Objectively Validated Assessment/Reporting

Professionals demonstrate nonmaleficence and beneficence and promote justice in clinico-legal settings by conducting unbiased examinations and testifying honestly. Sweet and Moulthrop (17) have offered relevant and pointed self-examination questions that should be utilized when conducting assessments in adversarial contexts. These contain questions for procedural conduct, including, for example, favorability of findings to referral source, comparison of current findings with base-rates, and presence of emotions and actions suggesting advocacy. They also contain questions for written reports which include whether a panel of peers / experts would agree with findings and conclusions; whether contradictory facts and evidence were included or excluded; and whether exaggerated or dramatic descriptors were employed. Thus, the merits of a report might be determined in part by whether opinions flow logically from findings or seem to be pre-formed, whether equivocal test results (i.e., from high false-positive radiological, laboratory or neuropsychological tests) are appropriately employed to inform or merely selectively chosen, overweighted and exploited to persuade; and whether terminology was dispassionate, measured and proportionate; or emotionally charged and inflammatory.

Lees-Haley (18) has suggested that, in addition to self-examination, examiners should develop and employ externally validated safeguards to increase the probability of objectivity. Until such safeguards are developed, proposed guidelines (14, 19–22) offer good starting points for attempting to maintain examiner objectivity.

### Avoidance of Outcome Dependency

When the definition of success of two groups of professionals differs dramatically, their ability to work together on a project will be very limited. Hence when plaintiff lawyers define success as the development of a case capable of attracting a large settlement, no matter how modest the TBI impairment sequelae and how high functioning the claimant, then the report of the clinician who defines success solely by expertise, objectivity, and candor, will not be well received.

Attorneys must answer to their clients, who require them to be advocates and to maximize the benefits at outcome: it is natural that such attorneys will seek out experts whose viewpoints are more likely to be strongly supportive of their clients' cases, irrespective of case merits. Therefore, unless the referral is by mutual consent of the parties, or arises from the court itself, or unless the identity of the referral source is masked, the examiner must deal with the reality of being cognizant of the referral and payment source, and associated potential disincentives to full candor.

Unfavorable examination findings may trigger an undesirable set of consequences such as the attorney's inability or refusal to pay for services provided if the case is 'lost', or loss of further referrals by that attorney and perhaps his/her colleagues, with consequent decreased clinico-legal income. Given the restrictions in reimbursement in other areas of healthcare, there are considerable pressures and reinforcements that serve as disincentives to producing 'unfavorable' findings. Consequently, subtle processes, such as suggesting limited reliability/credibility to contradictory information sources and making selective interpretations in unclear situations, would seem especially vulnerable to influence. Subtle- to not-so-subtle influences involving the preference/need of the referring attorney may also predispose examiners to unidirectionally interpreting all findings or to advancing unusually firm or unequivocal views. Such influences represent threats to objective, ethical practice and to professional credibility.

Many jurisdictions have made, or at least contemplated, practical attempts to neutralize the potential for influence related to outcome. In 1996 the Provincial legislature of Ontario created a system of Designated Assessment Centres (DACs). An impartial governmental team would randomly assign a case to Center, where expert evaluators were expected to make benefit determinations while adhering to standards of neutrality, transparency, cost-efficiency and timeliness. Competence and cost were monitored, and Center administrators were held accountable for quality assurance, always subject to loss of designation. Within this system, evaluator selection was independent of either party; fees were predetermined and payment was assured. Evaluators were highly insulated from outcome, by virtue of a random referral process in which determinations had no influence on future referrals, payment arrangements or income. The primary determinants of case load related to delisting from DAC rosters for persistent failure to maintain expertise, timeliness or neutrality. Unfortunately, the DAC system fell victim to political 'reforms' and was eliminated in March 2006 in favor of an Insurer Examination system.

### Neutrality and Selectivity in Office Practices

Avoiding the *appearance* of lack or loss of Neutrality is often as important as the actual state of neutrality. Both

perception and existence of neutrality require active as well as passive measures, more easily achieved in group practices than for the individual practitioner. A balanced and fair, written referral policy is a reliable passive approach. The appearance of neutrality of a clinician is reinforced by the appreciation that the clinician is prepared to evenhandedly accept suitable cases from plaintiff and defense.

High selectivity in case acceptance can indicate the clinician's commitment to working strictly within scope of practice, and general or special expertise. However, it can also work against positive perception. Thus, a consistent policy of accepting only severe TBI cases, evenhandedly from plaintiff and defence, signals a neutral interest in a specific condition suitably challenging to the clinician's expertise, while by contrast an indiscriminate policy of accepting 'all comers', including cases of dubious brain trauma or impairment, or worse, a selective policy of taking primarily dubious claimant cases, may signal a pattern of self-marketing, as an advocate and "case builder".

Clearly, perceived neutrality is enhanced by the degree of perceived distance between the referring party and the clinician. Thus, selectivity within a group practice may be particularly significant. While the group may have an open policy on acceptance of referrals, there may be an internal agreement (1) to randomly assign cases, or (2) to 'stream' on the basis of individual member expertise and experience. Additionally clinical examiner groups may have their staff mask all information about the referral source, substituting a briefing paper, which sets out the goals of the evaluation without specifying whether the referral is for plaintiff or defense sides.

In some cases, in order to resolve clinical ambiguities, establish the current scientific understanding, or otherwise clarify issues before trial, the presiding judge may select an examiner and order an expert examination, or may order the parties to jointly select a mutually agreeable examiner. Either approach may significantly advance the process of settlement through neutralization of the expert referral process.

Attorneys who recognize the potential that their act of referral may itself 'taint' the expert should carefully craft the referral request in neutral terms to identify the issues that remain in dispute, and fairly set out the difficulties existing between the parties owing to their understandings and positions, requesting diagnostic or management opinion or clarification of existing opinion so as to best inform the parties and the triers of fact.

Unfortunately, a clinician's commitment to neutrality may be compromised by a selection process which is intended to 'take advantage' of clinical proclivities; the clinician then becoming the unwitting tool of advocacy. Attorneys are often well versed on which clinicians consistently favor a certain scientific theory or a particular threshold, or test finding. Thus, in order to garner support for a weak case, an attorney may refer to a clinician known

to uncritically accept all complaints and claims as entirely reliable. Similarly, in order to attack a strong case, an attorney may refer to a clinician who is an unremitting skeptic of all subjective matters and prefers to rely solely on the results of MRI and objective clinical findings.

Toward the goal of maintaining examiner objectivity, Brodsky (19) suggested that examiners calculate an *objectivity quotient* in order to quantify the degree to which the expert clinician's findings have been in agreement with, or different from, a referring attorney's position. The objectivity quotient is calculated by dividing the number of cases in which findings support the referring attorney's position by the total number of cases the clinician has been involved in as a consultant and/or expert. A cutoff score of 0.7 has been proposed for potential examiner bias.

### Expert Witness: Trial Consultant Role Boundaries

Experts must be vigilant against the possibility that their assistance of the retaining party in the clinico-legal aspects of a case could extend into ethically questionable behavior. Expert Witnesses must not go beyond providing their own independent and objective opinion about the examinee. There should be no crossing of the line that separates disinterest in outcome from outcome promotion.

It is proper for the Trial Consultant to focus on outcome and to work towards optimization of outcome terms satisfactory to the referring party, but nevertheless based on the evidence and merits of a case. He/she is expected to assist with strategic or tactical "trial preparation" by participating in efforts to accumulate a complete case database, and to effectively cross-examine concerning the procedures, opinions or other testimony of clinician witnesses. However, partisan criticism against experts and advocacy for the adversarial attorney team in its battle to "win" through impeachment (e.g., by preparing deposition or trial questions or strategy or discussing stylistics or cases beyond the current one) strains ethical clinical boundaries. An ethical Trial Consultant assists with identification of the strengths and weaknesses of all opinions, and advises in balanced fashion on the current science.

It is ethically inappropriate for any professional to participate in preparation of *ad hominum* personal attacks, or in selective, misrepresentative citations of literature, or misuse of statistical analysis, with the ultimate intention of confusing or misinforming the triers of fact.

## CONDUCTING THE CLINICO-LEGAL EXAMINATION

### Establishing Ground Rules in Advance

Most commonly, referrals of a strictly clinico-legal nature come from attorneys, insurance companies, and other

third party payors and are clearly intended for use in litigation. The clinician has a clear opportunity to decide on involvement. By contrast clinical referrals from physicians or other referral sources may start out as requests for consultation or for participation in caregiving, with the clinician's caregiver involvement making inevitable some linkage to any subsequent litigation process. Indeed, a 'Trojan horse' phenomenon is sometimes seen, in which the clinical referral for consultation is in fact instigated or influenced by a plaintiff lawyer, whose intent is either to later obtain a relatively inexpensive expert clinicolegal report, or ensure the clinician's involvement in an eventual trial, or at least ensure that no other party can obtain that clinician's services as Expert Witness in the case.

In a clinicolegal referral it is critically important to establish the basis of the referral and the parameters of anticipated or permissible interaction with the evaluatee, since many patients confuse the roles and may resent or even actively complain to regulatory boards about perceived failure to give the advice or care expected. This is particularly important for the patient with impairments of cognition, where concrete thought or memory deficits reduce the ability to appreciate the distinction between caregiving and independent assessment.

Equally, prior to carrying out an independent evaluation, it is important to ensure that the referral source appreciates that no therapeutic relationship of advice or care will exist. The evaluator should not be expected to provide direct advice or care to the examinee at the time of the evaluation or at any time thereafter, and there is no ongoing relationship or obligation to the evaluatee beyond normal ethical and professional behaviour. As a corollary, it is improper for an evaluator to offer direct advice following an IME, and instead this potentially disrupts existing therapeutic relationships and thus is an ethical violation.

In parallel, the source of funding for the referral must be carefully established. Seeking concurrent fees from both a clinicolegal referral source who requested an independent examination along with billing any other party such as a health care insurer, has been referred to as 'double billing' or 'double dipping', and is unethical.

### **Communicating Ground Rules to the Examinee**

Examinees very often present for independent examinations with ambivalence, anxiety, or even distrust (19, 21–23). For the TBI patient, such psycho-emotional states may be superimposed on neurological impairments of cognition, emotion, or behavior; physical impairments; and/or financial, vocational and/or interpersonal difficulties that are the reasons for the examination. Apprehension may be due in part to inaccurate or incomplete information provided to them by their attorney, family members, treating health professionals, or others regarding the purpose and nature of the independent examination.

Not uncommonly, the referral by an insurance company for clinicolegal examination is interpreted by the evaluatee as hostile in nature, implying or even seeming to overtly accuse the evaluatee of unreliability or deception, or the attending clinicians of incompetence. For example, the lack of proper understanding of the nature of an independent clinicolegal evaluation accounts for the majority of all complaints to the College of Physicians and Surgeons of Ontario, with the most common complaint involving the perceived improper behaviour of the physician in either not offering or refusing to provide, on request, advice or prescription.

The examiner who provides accurate information about the purpose of the examination and the procedures to be employed at the outset of the evaluation will likely help to reduce the examinee's anxiety and distrust and to increase his or her cooperation. Recognizing the potential for anxiety that is inherent in such examinations and emphasizing the objective nature of the examination should serve to increase the examinee's comfort level and perception of fairness, while fostering reliable performance. Clearly, as Binder and Thompson (24) have noted, in the case of the neuropsychologist but with general application to all clinicians, one must attempt to minimize any potential discomfort associated with the examination.

The Canadian Society of Medical Evaluators has developed educational pamphlets specifically for dissemination by clinicians or insurers to evaluatees. Separate pamphlets were prepared to meet the somewhat differing circumstances of physical medicine and psychiatric independent examinations. By anecdotal reports, its use by CSME members has been associated with a marked decrease in regulatory body complaints, and/or facilitation of complaint resolution.

### **Response Bias**

Response bias is the deliberate or inadvertent presentation of oneself as more or less impaired than one actually is. Its presence must always be considered, assessed and commented upon as it might pertain to the clinician's findings, and in regard to the findings of other clinicians. This provides the report's readers with a reference point as to how fairly and competently this confounding element was assessed, what finding was made, and whether the implications were considered and applied to the balance of the report. It may serve to provide a basis of understanding for some differing clinical opinions.

Employing formal and informal means of assessing response bias, followed by formal, structured reporting of related findings is a critically important component of a comprehensive TBI evaluation. The official position paper of the National Academy of Neuropsychology on symptom validity testing now posits both that response bias assessment, and any specific symptom validity tests deemed necessary for evaluation of symptom validity, is

medically necessary (NAN Position paper reference) National Academy of Neuropsychology Position Paper: Symptom validity assessment: Practice issues and medical necessity: Official Statement of the National Academy of Neuropsychology, Approved by the Board of Directors 2/28/05. [www.nanonline.org/downloads/paio/Position/NANsvt.pdf](http://www.nanonline.org/downloads/paio/Position/NANsvt.pdf). Retrieved 4/21/06 (25). However, the examiner should exercise caution in regard to going further, by inferring motivation - the intent and goal of the evaluatee. The evaluator should instead discuss the differential diagnostic list of potential sources of the unreliability detected: including inadvertency, medication, pain, fatigue, personality or pathopscho-emotional mechanisms. As a corollary of a careful assessment for response bias, the examiner will be in an enhanced position to consider the reliability and validity of the apparently abnormal findings of those clinicians who did not look for inconsistencies or otherwise allow for response bias. (See Chapter by Martelli, et al. in this text on response bias assessment, and National Academy of Neuropsychology Position Paper on symptom validity testing) National Academy of Neuropsychology Position Paper: Symptom validity assessment: Practice issues and medical necessity: Official Statement of the National Academy of Neuropsychology, Approved by the Board of Directors 2/28/05. [www.nanonline.org/downloads/paio/Position/NANsvt.pdf](http://www.nanonline.org/downloads/paio/Position/NANsvt.pdf). Retrieved 4/21/06 (26).

As a further quality control measure, prior to examination the evaluatee should be given an explanation of the anticipated examination process; as a component of this description, the examiner should emphasize the importance of displaying one's real capacities, including consistently putting forth one's best efforts throughout the examination. It should also be explained that the consistency and extent of the examinee's effort and degree of disclosure will be assessed and may impact on the examiner's rating of reliability.

It is ethically necessary to give the evaluatee notice before the evaluation that response bias and reliability may be tested. It is not necessary or even advisable to disclose the nature of the testing, or that there may be use of informal, as well as, formal means. However, it is imperative that the evaluatee also understand that pain, fatigue, confusion, memory lapses, or other neurological impairments will not be regarded solely as evidence of lack of cooperation or effort.

### **Perceived Control and Quality Assurance**

It is important for the evaluatee undergoing a clinicolegal examination to retain a sense of control over the proceedings, including to a reasonable extent the right to control its pace, and the right to ask why a particular question is being posed or test procedure performed. The evaluatee has an absolute right to decline to proceed with a given

question, exam procedure and/or the evaluation itself. Within reason, accommodations should be made for breaks to use the restroom, or to rest due to fatigue and/or the need to take medication. It is often instructive to encourage the evaluatee to comment during and particularly towards the end of the evaluation if any element of questioning or testing was new, unfamiliar, or omitted. The examinee should be informed of the importance of reporting any sense of difficulty or distress to the examiner in 'real-time', not later.

It may also be necessary to notify the evaluatee of "zero tolerance" rules regarding any inappropriate verbal or physical behavior, and of potential negative inferences from lack of cooperation, or from premature termination of the evaluation, without reasonable basis. The expert examiner must always allow for the possibility that in TBI evaluation, response bias, lack of consistent cooperation, or problematic verbal or physical behaviors may be the inadvertent and uncontrollable consequences of pain, fatigue, medication, seizure, or behavioral disinhibition.

### **Confidentiality Issues**

The clinicolegal evaluation is one in which a limited duty of confidentiality is owed to the evaluatee. The referring party is entitled to full disclosure of anything learned by the examiner at any time during the evaluation. The evaluatee should be under no misapprehension that the evaluator can be held to instructions of 'strict confidence', including disclosures involving sexual orientation; sexual, physical or substance abuse history; STDs or abortion.

The absence of a therapeutic relationship does not prevent the examiner from communicating verbally or in writing with a treating clinician, regarding any concerns or suggestions, particularly emerging issues such as suicidal rumination or inappropriate regimen or dose of medication. A memo must be made of the date, name and content of any verbal communication. Written communication by mail, fax or email, must be retained with the file. The appropriate means of communication will depend upon the nature and priority of the circumstance; a note should not be entrusted to the evaluatee if there is any doubt as to whether and when it will be delivered or concern over the evaluatee reading the contents.

### **Informed Consent**

Once the examinee understands the purpose of the examination, the process of the examination, rules of disclosure, expectations for cooperation and effort, evaluatee rights, and the extent of feedback regarding the results of the examination, the examiner should invite questions and provide further clarification as needed. Only after these issues are seen to be clearly understood by the examinee should his or her informed consent to participate be sought. Consent

forms are necessary to document the examiner's efforts to inform and the examinee's consequent understanding and agreement. In addition, consent forms can facilitate communication between examiner and examinee. A checklist can be incorporated into the consent form, allowing examinees to systematically consider, seek clarification if necessary, and then indicate their understanding of each major point by initialing each point on the list and/or signing the bottom of the form along with a witness.

Clearly, informed consent cannot be obtained and should not be sought directly from evaluatees with marked cognitive or communication disorders or from minor children. In such situations, consent must be obtained from the individual's legal guardian. In some circumstances the evaluator should seek written proof of guardianship.

### **Third Party Observers—Direct and Indirect**

The issue of allowing a person other than the examiner and examinee into the examination session is complicated. Without exception, the physician examiner should consider use of a staff person as chaperone, to assist and to attest that no inappropriate conversation or action took place. In many jurisdictions it is the right of the evaluatee to designate another, suitable third party to be present for his/her comfort and/or as an observer, a witness to what transpires.

Where the evaluator retains a veto right, persuasive pro and con arguments can be considered: a 'pro' argument may exist when the claimant can be expected to be exceptionally apprehensive unless accompanied. In fact, the issue often benefits from avoiding the polarization of the "either/or" proposition, and instead clarification of who should be able to observe and in which settings and with what relative benefit to evaluator or evaluatee. The evaluator should however bear in mind that, oftentimes, skilled third party witnesses such as nurses are specifically designated owing to their ability to testify as credible observers about what happened during the examination. Evaluators should always keep in mind that they almost always retain the option of declining the referral if any of the imposed conditions of evaluation appear unacceptable, including designation of a third party.

A claimant-designated third party is, ideally, a passive witness to the procedural events, with no role beyond reassurance of the claimant. No third party should ever be permitted to participate, advise or interfere unless invited to do so, and no third party disruption that compromises the quality of the evaluation should ever be tolerated.

Several authors have presented reasons why the presence of a third party may be contra-indicated during examinations in which standardized tests are used. These reasons include (a) compromise of test security and subsequent misuse of tests, (b) invalidation of results due to tests not having been standardized for third party presence,

and (c) invalidation of results due to social facilitation, (27–31). A policy statement from the American Academy of Clinical Neuropsychology made the distinction between involved observers and uninvolved observers (32). An involved third party observer is someone who has some investment in the outcome of the examination, whereas an uninvolved third party has no stake in the outcome, and instead is strictly a source of emotional support to the evaluatee. In contrast, a NAN policy statement distinguished between settings, with third party observers being acceptable in clinical settings for training purposes but unacceptable in forensic settings (29). Issues of observer training, observer involvement, and examination context have all been considered relevant in the debate on the appropriateness of having a third person present during neuropsychological examinations.

The Canadian Society of Medical Evaluators (CSME) has developed guidelines for assisting in the determination of 'who and when' for the presence of a third-party, where there is a choice. The Society recommends that its members maintain a written protocol, not only to assist them but also to demonstrate to others the rational basis and consistency of their decisions. Thus, one's protocol might set out that a chaperone will always be present; in addition, a first order family member is mandatory for examining any minor. The Society notes that a medical professional such as a nurse is preferable to a non-family lay third party, as an evaluatee-designated observer, owing to insight into what constitutes acceptable questions and routine examination practices. Any third party must agree to be placed outside the visual field of the evaluatee, to prevent any cueing or other interaction.

We would also note that there is both extensive experience and now some recent literature to support the position that despite best intentions and circumstances, examinee performance may be adversely affected by observers, even or especially when they are their own family, friend or case representative (e.g., case manager or lawyer). Negative consequences of third party observers become difficult if not impossible to factor out when considering apportionment of sub-optimal or otherwise misleading performance.

Videotaping and audiotaping are seemingly less intrusive means of monitoring the examination process. However, these methods of observation can also introduce atypical dynamics into the examination process (analogous to the abruptly altered behaviours evident in home movies or the 'frozen' look of one's colleagues, stuttering into a reporter's microphone. Evaluatees may 'act out' for the future audience, or may withhold candor anticipating abreactions of family viewers. At particular disadvantage may be certain TBI evaluatees, who are anxious about being perceived as abnormal, embarrassed by paretic facial appearance or speech impairments, or behaviourally disinhibited.

Examiners too may experience alteration of well-established, efficient and effective routines, due to inadvertent effects on body language, tonality, questioning style, or pace (unnaturally slow or hurried).

The setting too is usually not ideal, since the medical office is neither a recording studio nor a well-lit television studio complete with camera- and soundmen. People mumble, tummies rumble, clothes brush on microphones, clocks tick, computers hum, tapes run out and batteries fail. Voices may be non-uniformly distorted in tonality or nasality, or unnaturally amplified or suppressed, subtly influencing the viewer long accustomed to the quality of TV and movie. Voice activation, ambient noise suppression mechanisms, static, activity outside the microphone or camera range, or involving soft speech, shadows or reflections, may cause an audio or video to fail to clearly capture words or events that the examiner observed and found sufficiently relevant to make notes about. This may create a 'Hobson's choice' dilemma for the reviewer, compelled to assign relative weight to the electronic record and to the version of events noted and/or recollected by the examiner.

Preliminary studies suggest that formal testing results may be negatively affected by the presence of observers or recording devices, in a selective, non-uniform fashion. In one study, audio recording appeared to negatively affect verbal learning and recall but not motor performance (33). In another, video recording negatively affected immediate and delayed memory performance but not motor performance or recognition memory (34). Such studies indicate that both direct observation and indirect observation via recording devices may have a negative effect on psychological test results, posing a threat to the validity of tests developed without scrutiny for such variables, and placing in jeopardy the reliability of the test results and the relevance to the specific evaluatee of subsequent interpretations of test results.

### **Selection of Assessment Procedures**

It is routine for TBI assessment reports to be closely scrutinized by all parties, and actively critiqued, particularly by opposing counsel who may retain professionals for that specific and sole purpose. The examiner should be aware that every aspect, including the selection of questions and tests, the method of carrying out the tests, the findings, and their interpretation, will be subject to retrospective analysis and possibly to aggressive criticism. Clinicolegal examiners do not have the option of citing as excuses the practical exigencies of daily practice; examiners are expected to set aside as much time as necessary to carry out all relevant testing, to review all potentially significant documentation, to seek a complete data base and only then to comprehensively analyze data and formulate opinions without urgency. Nevertheless, even the most thorough and methodical approach is not safe from criticism.

Due to differences of opinion regarding optimal methods of investigation, no set of medical, psychological or neuropsychological test procedures is beyond the critic's reach. However, criticism is far less successfully applied to tests and assessment procedures that are standardized, have a strong research base for relevance, validity and reliability, are well accepted and commonly taught and used within the profession for the same general or specific purpose, and have a history of acceptance in the courts.

Testing must comply with accepted standards and protocols; to further ensure the perception of even-handedness the clinician may benefit from consistently applying the same test protocols to all patients seen with the same condition. (e.g., a medical evaluation of functional recovery, for all TBI claimants whose residual symptoms include excess daytime fatigue, might routinely include an Epworth Sleepiness Scale for severity quantification, and a differential diagnostic screening for comorbid but non-traumatic nocturnally disruptive conditions such as sleep apnea or benign prostatic hypertrophy).

It is appropriate to omit or take particular precautions with administering, considering and, reporting tests that have poor validity and reliability – which nevertheless remain in widespread usage. To a reasonable extent the clinician may need to explain why each such commonly used test was not employed, and what other tests was substituted and with what advantages.

Not uncommonly, rather than developing and defending their own protocols, examiners rely reflexively upon published authorities, without ensuring familiarization with both strengths and weaknesses. One widely used reference is the American Medical Association Guides to the Evaluation of Permanent Impairment (GEPI) (35), which throughout its' five editions to date (2001), has provided, in substantial detail, sets of standardized measurement procedures; describes means of determining the tolerances of intra-observer variability; and offers alternative methods to direct measurements – such as Diagnosis Related Estimates (DRE). Critics of the GEPI complain that the authors do not adequately acknowledge the limitations inherent in consensus-based guidelines, the dearth of strictly validated sets of test processes for impairment measurement in the various bodily Systems, lack of specific identification, correlation and weighting of impairments to various instrumental and personal activities of daily living (ADL), or the perpetuation of confusion regarding such terms as impairment and disability, among numerous other limitations.

The examiner should acknowledge limitations in current knowledge. Moreover, if, under special circumstances, experimental procedures or normative data not representative of the examinee's condition are used, test results must be interpreted cautiously, and clear documentation of these procedures and the rationale for their use and potential for erroneous labelling (e.g. selectivity and specificity) should be provided.



There is a danger in utilizing test procedures that are anecdotal in origin, such as those one might develop over the years within one's own practice, or might acquire from mentors and colleagues. Proving validity and reliability may require blind testing of substantial groups of subjects, with comparison of results and interpretation to tests of established reliability. Caution should be employed in the use of tests which may be well accepted in certain domains of impairment evaluation, but have no known reliability or usefulness in other domains. For example, JAMAR grip testing is routinely employed in functional capacity testing for chronic pain and orthopaedic impairment cases; consistent, full effort is required for the results to be valid for peak strength. Falsification is a serious concern. The Rapid Exchange Grip (REG) test (rapidly alternating right and left hand grips) has been found to be very difficult to falsify and REG results are considered relevant to the question of whether full effort was consistently exerted, and thus whether the measurements obtained on routine JAMAR grip testing were representative of peak strength. However, the typical test subject has no neurological impairment of coordination, pace, proprioception, or motor tone. The validity and reliability, for applying the REG to TBI patients with hemiparesis, spasticity, or apraxia, remains insufficiently tested and thus unknown.

### **Delegation in Testing**

Delegation of testing to one's subordinates is a source of potentially critical flaws. Delegation may be found in certain procedures such as electromyography, neuropsychology, or even interview taking, test administration and/or physical examinations. However, delegation of interpretation is never acceptable. Standardizing methods, order and choice of procedures, ensuring training and maintenance of competence, and minimizing or excluding subjective input are all elementary requirements of appropriate delegation.

It is self-evident that delegation of interviewing not only reduces the evaluator's total contact time with the evaluatee but also reduces the dynamic interview element of following leads created by hesitation or special comment, facial expression, vagueness and/or ambiguity. On the other hand, the accusation that the interviewer rushed the interview or selected questions that precluded the evaluatee from providing complete or balanced information is offset when an assessment is allotted a standard amount of time and pace, and a standardized, core set of questions and checklists is employed, an essential approach to TBI cases.

While it would seem that there is no 'right' answer applicable to all clinicians, or all circumstances, the general principles remain applicable: the evaluator is ultimately responsible for the comprehensiveness and validity of all data collection, and for its interpretation. When it can be shown that more direct evaluation or testing

time, with either a more standardized or a more dynamic, responsive approach, would have led to a better outcome then valid criticism can be applied; and the weight given to the examiner's opinion proportionately diminished.

## **TBI CLINICOLEGAL REPORTING**

### **Critical Components**

The report of any comprehensive independent examination should include the following: demographic details; referral source; party responsible for payment; basis of report (file review alone, claimant alone, family interview etc.); documents requested and reviewed; documents requested but not received; history of present illness; past medical history; family medical history; psychosocial history; educational history; vocational history, including military history if applicable; legal history, including both civil and criminal, as applicable; review of medical systems; comprehensive review of examination findings, including pertinent negative findings; validity of findings, including results of response validity assessments; diagnostic impressions; opinions regarding current and expected future status; maximum medical improvement (MMI) and prognostic opinions; causality and apportionment opinions; risk and restrictions as related to the injury or disease in question; recommendations for treatment or further diagnostic studies; degree of confidence in findings and conclusions; and relevant appendices, clauses and caveats. All opinions should be qualified by degree of certainty (e.g. likelihood with greater than 50% confidence is termed 'probable', while 50:50 or less is termed 'possible'; strong qualifiers of confidence in common clinical use include 'balance of probabilities' and 'reasonable medical certainty').

### **Review of Documentation**

A critically important component of the report is the thoughtful review of specific findings and opinions from medical records. Although some readers with access to all medical records may find this integration of information to be repetitive, the independent examination report is sometimes the only place where a comprehensive integration of the totality of relevant information can be found. A review of background information and medical opinions serves to (a) demonstrate that the records were reviewed, (b) establish the temporal relationship of complaints to the reported injury, (c) facilitate an analysis of the symptom profile in relation to the type of injury being claimed, (d) evaluate the consistency of symptom reporting over time and across contexts, (e) evaluate indicators suggestive of recovery, if present, over time, and (f) provide clear delineation of the inferential reasoning process employed.

It is important to identify and discuss the potential relevance of any materials or other sources of information

not available to the examiner for review. Not uncommonly in TBI case work, this may include prior records which might indicate fetal problems, birth trauma, childhood trauma or infection. School records of achievement and behaviour, as well as any learning deficit, and any intelligence, personality or aptitude testing, can all be of enormous value in appreciating acquired deficits.

There may be situations in which the examiner is not provided with all consultant, treatment or investigative records related to a case. Such restrictions limit the confidence that the examiner can place in his or her own findings. It is relevant to realize that the same shortcomings of database were likely in effect when other professionals reviewed the case, and the same reservations can be fairly applied to the balance of opinions already advanced by others and thus to be found in the file.

Materials not provided can be ranked as to potential importance to report completion. Thus, material may be deemed either Critically Required for a competent evaluation, or merely of Potential Value to clarification or confirmation of existing evidence.

Critically required documentation contains data expected to be of considerable importance, such that without access it would be impossible and improper for the ethical, expert examiner to offer informed, authoritative final conclusions. Thus, certain past medical records may contain information critical to establishing date of onset or other causation-related facts; disinterested clinical or other observer records may enhance one's understanding of the nature and sequence of an event, or provide independent sources of information about daily function, to supplement the narrative interview of the evaluatee or family members. As a specific illustration, when a student suffers a TBI and claims subsequent impairment of academic abilities, corroboration or clarification may be critically influenced by a direct review of prior as well as subsequent academic records of attendance, behaviour and marks, essays and test answers.

Materials of potential value might include documents whose review would be prudent, to ensure thoroughness. For example, one or more 'silent periods' in which there are no entries in either prior or post-injury medical records provided, out of keeping with established care-seeking patterns and/or spanning long periods of time, might well be corroborative of claims of interim good health or stoic self-reliance; alternatively these chronological 'black holes' may reflect undisclosed health care in the same or another community, or even episodes of incarceration. Completion of the healthcare record may reveal unsuspected premorbid or comorbid social, familial, legal, vocational, financial, psychiatric or physical problems - including instances of prior traumatic, vascular, infectious or other brain injury.

It may also be prudent, and sometimes it is critically important, for examiners to request (where appropriate

to scope of practice) raw data from certain testing procedures or hard copies of pertinent radiologic studies and to consider seeking opportunities for corroboratory interviews to round out information collection.

Regarding the overall analysis of assembled information, including examination findings already carried out and documented in prior records, it is reasonable for the examiner to comment on the appropriateness of diagnostic procedures and processes employed, and the consequent reliability and validity of the findings, including estimation of the degree to which the measures used were specific and sensitive to the condition being examined, and the degree of confidence that can be placed in the interpretations and opinions presented. Many examiners feel uncomfortable commenting on the methods and/or conclusions of their colleagues, especially in the absence of the raw data. However, balanced, expert, critical reviews are essential to promotion of thoroughness and objectivity and thus are essential to quality assurance in examinations in clinicolegal settings. Each step in the examination process should be open to critical evaluation in the context of the case and the research literature. The reviewer needs to establish that there has been appropriate choice and administration of tests, proper and balanced interpretation of all of the test data, appropriate data assembly, and sufficient and unbiased reporting of all data. However, in the absence of required raw data, informed critical review may not be possible and report completion may have to be suspended.

### **Completeness of Records and Disclosure of Findings**

Clinicolegal examinations require complete documentation of all procedures conducted and results obtained. The examiner must create appropriate documentation in the expectation that one's records will be critically reviewed by independent professionals both within and outside of one's areas of professional specialty. In addition to formal reports, all information generated during an examination, including handwritten notes and test protocols, may be subject to review by others. Some practitioners advocate for inclusion of all handwritten notes as part of their final report, including copies of all testing results (sans any copyrighted materials). Notes must be legible and abbreviations universal or otherwise unequivocal in interpretation.

### **Drafts and Final Reports**

Ethical practice requires that examination findings be presented objectively, fully and carefully in a report, that no inaccurate documentation be generated, especially for information not obtained or findings not made, with no salient information excluded. Notably, distinct from internal drafts, some professionals will release preliminary reports prior to preparing a final report. Like most other

areas of practice, the reasons for such procedures and the manner in which they are handled determine the degree to which these may potentially challenge ethical principles. Certainly, offering the referring party one or more drafts and soliciting 'feedback' will introduce potential for perception of, as well as actual, biasing of the final report.

Distinct from the above might be a circumstance in which a preliminary report is released to apprise the parties of the status of a continuing evaluation, including justification for requests for further visits, tests or documents. Similarly, a preliminary draft may be released to the referring party along with a specific request for confirmation that all issues of concern have been addressed fully and clearly. It follows that no material alteration in the findings or conclusions, reflecting the referring party's censorial or advocatorial preferences should appear in the subsequent final report.

A report may be released in stages, involving independent components. Any released report component should be considered final for its purpose. Thus, while pending neuropsychological testing or current school year marks prevents completion of a report on spectrum and severity of impairment from TBI, an initial report may be released in which the evaluator addresses questions of causation, mechanism, and diagnosis.

The temptation to request 'tweaking' (alteration to enhance value) of the final report can be irresistible to advocatorial referring/paying parties. Once a final report is issued, the examiner must carefully consider whether and how to respond to any subsequent requests for alterations by the referring party, the evaluatee or others. The examiner should always insist on first receiving any such request in writing. Some requests for changes are fully justifiable, including typographical, chronological or factual errors. It is also appropriate to respond to requests for clarification or amplification or requests of similarly constructive nature, while avoiding altering or debating the findings or opinions. Common instances include requests for clarification of technical terms or reasoning for the court, or for the clinician's opinion to be stated in accord with the formulaic language of legislation – as an example, it may be required that the report unequivocally establish whether impairments meet a verbal threshold such as 'substantial', 'permanent' or 'severe'; an opinion regarding a treatment may require specific reference to whether it is both 'necessary and reasonable'.

Options for rectification of factual errors include: 1) attaching an amended page to the report, 2) marking through the incorrect portion of the report by putting a single line through the incorrect material so that the original can still be read, and then writing (and initialing) the correction in the space above the line, or 3) producing a corrected version of the report and documenting the

rationale within a cover letter. All draft and amended versions of reports, (other than those which fall under solicitor-expert privilege such as notes and other work-products made solely for purposes of discussion with the referring party), should be maintained and produced upon request, as a proof of credibility. Self-tweaking an unsupported conclusion in advance of report release is not ethical; the examiner's report should closely correspond to his/her written records.

### **Use of Disclaimer Statements**

It is recommended that examiners have a disclaimer at the beginning or end of their reports reiterating the basis of the report and the opinions, as related to his/her qualifications. It should be noted that all opinions were provided with the strength of "probability", (greater than 50%) unless otherwise indicated. It is also advisable that examiners include a statement noting that their conclusions are based, in part, on the assumption that the materials provided for review are complete and correct and that if any additional information becomes available at a later date, opinions may be subject to change. It will be relevant to state, in the case of a file review, whether the opportunity for direct clinical assessment was offered, and to what extent such an opportunity might have resulted in a different set of conclusions and recommendations. It is relevant to state the nature and source of the referral, and any special instructions. For example, the examiner may wish to clarify that referral originated with plaintiff's counsel, relating to an MVA claim of a certain date, and that the referral request included a specific request for, or direction to deal only with, the management and prognosis of post-TBI seizures.

It is relevant to declare the absence of any known conflict of interest, or to explain how any potential conflicts were identified and addressed. For example, where two physicians work in an assessment centre, and one has been a treating practitioner, the second – in the role of independent examiner – should state that the case was never discussed between them; that the provision of a second opinion is common in medical practice; and that the examiner felt no reservations about discussing in his/her report any area of disagreement over diagnosis involving his colleagues.

## **USE OF EXPERT WITNESSES**

### **Expert Witness Fees**

Examiners are typically entitled to be paid at higher rates for clinico-legal work than for routine clinical services, owing to factors such as (a) requirements for an expanded, and specialized scope of knowledge and assessment skills; (b) special stressors and exceptional rigor required in maintaining the standards and following guidelines associated

with the litigation process; (c) the exceptional impact of such work on clinical responsibilities, including detracting from normal patient scheduling, and need for arranging clinical coverage, under circumstances of deadlines and unpredictable scheduling, etc.; (d) requirements for careful reading and note taking of substantial amounts of material; and (e) special precision in note taking and record keeping, report structure and preparation, proofing, correction, issuance, privacy issues, etc.

However, the creation of differential fee structures also creates a set of serious ethical issues. The primary concern, from the perspective of perception if not reality, is that differential fees introduce financial incentives, capable of exerting at least a subtle influence on the assessment process and formulation of opinions. The aforementioned must be counteracted by avoidance of any contingencies to the payment arrangement. Neither the size of the fee nor the timing and assurance of payment should ever be contingent upon the outcome of the case. The prospects of future referrals should not be contingent on favourability of opinion to the referring party. Such factors introduce bias, and such behavior is clearly proscribed in professional ethics codes.

Professional fees and terms should be agreed upon at the outset, involving mutual understanding of the feasibility and level of challenge of the type and scope of assessment contemplated. It is preferable that there be clarification of whether the fee is fixed or can be adjusted by the evaluator according to actual time, effort, and complications encountered during the assessment. Clearly, the establishment of fixed fees carries a greater perception of disinterest in individual cases; however, in order to avoid a negative bias against the referral source it is important to ensure appropriate adjustments for unanticipated and specially onerous circumstances such as urgency, need to seek further documentation, special research, language barriers, multiple or last minute cancellations and rebookings, or the especially difficult to examine evaluate. A reasonable compromise may involve either a set of standard fees that factor in exigencies, or a set of fee ranges, with terms for payment that do not change for particular referring parties.

The ethical burden can be somewhat alleviated by consistently referring to or utilizing published fee schedules and application guidelines from professional organizations. Ultimately the ethical test will be one of justification: can the evaluator explain how a fee and terms were developed within the context of a specific case. Clear records for that case and for comparable cases must be kept and kept available. Ethical behaviour therefore includes both internal consistency within one's own practice, and general consistency to the practices of one's ethical colleagues. In the latter context, ethical standards for medical experts can be expressed in terms of "reasonableness" and "consistency" of fees (36). In this case,

"reasonableness" is defined as the degree of similarity to fees charged by other examiners in similar specialties and localities; "consistency" is defined as the degree to which fees are compatible with other medical procedures of similar demand provided by the practitioner or his peer group, as well as for similar time units.

### **Court-Selected and Court-Hired Experts**

The use of court-nominated examiners is a potential solution to problems of partiality or advocacy. Recently, judges in Virginia have begun playing an increased role in the selection of experts for independent evaluations. Specifically, the presiding trier of fact may solicit a list or panel of experts from one or both counsel, from which the judge, or the judge in collaboration with opposing counsel, selects the professional to perform an independent evaluation. Although initially applied in situations where opposing counsel protested or attempted to block utilization of a particular expert, this practice seems to be expanding to other contexts.

Ideally, this approach to neutrality would find the trier of fact supervising or making the referral decisions, after a consensus process which ensures through careful selection that the experts will provide the court with objective, reliable, complete information. However, the experts must be commensurately remunerated for their consensually agreed upon capability, objectivity and ethics, and as a corollary their commitment to avoid the various degrees of "scientific perjury" which some other referral systems may encourage. Joint commitment to funding also ensures that payment is never contingent on outcome, and will not be subject to delay/discount/ bonus. There is the further attraction that the expert and the court are relieved of the time consuming and stressful process of impeaching experts by opposing counsel.

### **Admissibility of Expert Witness TBI Testimony**

The type of testimony that is admissible in court depends on the type of professional role that the expert plays in a given case (e.g., treating doctor/fact witness or expert witness). The treating doctor is permitted to present information related to clinical assessment and treatment conducted based on medical judgment of necessity and reasonableness. In contrast, the expert witness (in federal court and those state courts which accept Daubert (1)) may now be held to the Daubert standard (1) that scientific testimony must be supported by valid scientific theory or techniques. Specifically, Daubert requires that the scientific strategy or procedure has been tested, published under peer review, and is well accepted in the scientific community. Because the skills that make a good expert witness are not always consistent with reliance on "good

science”, the Daubert ruling seems to offer attorneys and the court a useful strategy for evaluating the merit of expert testimony. Given the complexity of many diagnostic procedures, particularly in TBI, scrutiny of the scientific methodology on which diagnoses are based is warranted, indeed essential.

### Monitoring Bias in Examiners and Examinees

In the context of personal injury examinations, clinical attribution bias refers to the consistent and predictable tendency to incorrectly attribute current symptoms to the injury or to the event in question. It typically results in a confounding of accurate diagnosis and appropriate treatment. Patients demonstrate inadvertent attribution bias when they incorrectly interpret periodic, common cognitive inefficiencies as being pathological, entirely attributable to a resolved Mild TBI. Ironically, attribution bias may interact with true neurogenic symptoms to increase impairment. Attribution bias can be influenced by others (e.g., family, attorneys or healthcare professionals) and, unfortunately, can also occur intentionally.

An examinee’s presentation and approach to test taking exists on a continuum ranging from valid to response biased. Due to the financial incentive to misrepresent one’s optimal performance during examinations in clinicolegal contexts, evaluation of the examinee’s response validity is a necessary component of the examination. The examiner must ensure that assessments, recommendations, reports, and diagnostic or evaluative statements are substantiated by sufficient information and techniques. Formal assessment of response validity is essential in order to increase the likelihood that interpretation of test data will be based on reliable results of valid tests; that is, the results will reflect the examinee’s true abilities and deficits.

Examiner misattribution bias represents a problematic source of error that can violate the core ethical principle of avoiding harm. Clinicians sensitized to the signs and symptoms of their particular specialty may misdiagnose or over-diagnose problems, with inadequate attention to competing explanations. For example, a Neurologist and a Psychiatrist, when confronted with a same symptom set, may be prone to speciality-specific diagnoses of, respectively, either brain injury or psychosocial distress (37). Inadequate rigor in developing appropriate diagnosis causes increased medical costs, inappropriate treatment, treatment failures and even chronic disability in the injured person. These errors can be prevented in TBI patients by comprehensive assessment that integrates data from observation, history, examination, radiological and neuropsychological testing and collateral sources, with a critical appraisal of base-rates of relevant symptoms (38–40) and careful differential diagnosis of all possible explanations for symptoms.

Chapman and Elstein (41) have discussed how biases can occur in the face of uncertainty in medical decision-making. Examiners can signal decision bias through any predictable tendencies: such as consistently discounting certain complaints as either not credible or unimportant; or to the contrary, consistently accepting all complaints uncritically, as self-validating (42). Compelling evidence of perceived expert witness bias is offered from a Federal Judiciary Committee sanctioned study, by Johnson, Krafka and Cecil (43), of active Federal judges and lead attorneys who presented the docket cases before them. For 1991 to 1998, the primary problem with expert testimony was experts who “abandon objectivity and become advocates for the side that hired them” (p. 5). Mean rating of partisan bias of experts on a 1–5 Likert rating scale was approximately 3.7. Clearly, there is a need for development, dissemination and universal acceptance of bias-avoidance guidelines, and of active promotion of objectivity and ethical conduct in clinico-legal contexts. However, when serious ethical violations are observed in colleagues, carefully deliberated action is indicated.

### ADDRESSING ETHICAL VIOLATIONS

Consistent with previously mentioned survey results, it is not uncommon in clinicolegal practice to observe apparently unethical work by colleagues. In order to protect patients, referral sources, and payors, and to preserve the reputation of one’s profession, it is necessary to actively but appropriately address potential ethical violations, when they are observed (44). Perhaps nothing so diminishes a profession’s reputation as the disclosure that the ‘community’ has known and tolerated or even covered up a colleague’s substance abuse, patient abuse, incompetence or unethical clinicolegal behaviour over an extended period of time.

Competency and objectivity may be the most frequently violated ethical standards. However, caution must be exercised in order to ensure that perceptions of incompetence or non-objectivity in a colleague are not overly reflective of professional or ideological differences. Certainly, there exist widespread differences of opinion in a number of areas of practice. Sensitivity to such differences is paramount.

However, the clinician who practices or makes judgments outside of even these diverse positions is at risk for justifiable implication of ethical misconduct if such practices or judgments cannot be defended through referral to published standards and guidelines, and recent research literature.

It is important to consider that consistent attribution bias may merely reflect a particular, sincere viewpoint rather than crass claim advocacy. In such instances, the identical attribution pattern can be expected no matter which side made the referral, or how sizable was the fee.

The authors acknowledge that the decision regarding whether or not to confront the poor judgment or apparent ethical misconduct of a colleague may be one of the more difficult professional decisions. That difficulty may be related to a number of factors, including uncertainty about the nature of the behavior and whether or not it occurred, as well as personal feelings toward the colleague, fear of retaliation, and uncertainty about how to address potential misconduct. However, the clinician must be candid with him/herself, as to whether such explanations and excuses are merely self-justifications for an attitude of complacency, or truly necessitate exemption from responsible actions.

Regulatory professional Boards and Colleges may bear some responsibility in this regard: by excess tolerance of either unethical behaviour or revealed instances of collegial complacency; or by lack of mechanisms for efficiently and confidentially receiving notifications of ethical violation concerns by professional colleagues and then promptly and professionally investigating them.

## CONCLUSIONS

Given the potentially devastating impact on all facets of life, TBI represent an very important subset of overall clinico-legal casework. Sadly, as with clinico-legal casework in general, TBI casework offers considerable potential for apparent or real ethical misconduct. The potential for harm is commensurately increased with patient vulnerability, particularly true of the TBI patient.

The ability to identify, for oneself, any areas of particular risk is the essential first step in avoiding not only actual ethical misconduct, but also the appearance of same. For competent professionals, the *loss of objectivity* is the primary risk factor for ethically compromised behavior.

In addition to competency and objectivity, a *lack of awareness and familiarity*: with relevant recent legal cases e.g., *Daubert vs. Merrell Dow* (1), with new methods and procedures, and with changes in relevant ethics codes, place the examiner at an ethical disadvantage. Thus, ongoing education on the application of ethical principles to clinico-legal practice is required for ethical professional behavior.

In order to promote consistently high levels of competent and ethical clinico-legal practice, the legal system must continue to establish *contingencies* and to use reliable *indices*, in order to genuinely increase the likelihood of objective examinations and testimony.

*Proactivity* is the proper response, when ethical misconduct is observed in one's colleagues. Appropriate steps need to be taken to prevent the abuse of the consumers of clinico-legal services and to promote the public's perception of fairness and consequent trust in the clinico-legal process. Ultimately, this is also of great service to one's profession, to one's professional colleagues, and to

the generation of clinicians who will follow, emulate and ultimately replace us.

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# 64

## Assessment of Response Bias in Clinical and Forensic Evaluations of Impairment Following TBI

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### INTRODUCTION

Evaluation of neurologic impairments and associated disability presents a significant diagnostic challenge. In cases of more catastrophic or functionally disabling injuries, the evaluations and opinions of different medical practitioners are often fairly consistent. In other cases, however, the evaluations and opinions of practitioners may vary widely.

Impairment and disability evaluation following neurologic injury typically involves such contexts as social security disability application, personal injury litigation, worker's compensation claims, disability insurance policy application, other health care insurance policy coverage, and determination of competence to handle finances or other important life functions (e.g., parenting) or decisions. Traditionally, these evaluations have fallen within the purview of the general fields of physical medicine and rehabilitation, neurology, neurosurgery, psychiatry, psychology and neuropsychology. More recently, and especially in cases of less catastrophic and more subtle cognitive impairment and disability, practitioners who specialize in brain injury evaluation and treatment are increasingly relied upon.

Impairment and disability evaluation may be one of the more misunderstood areas of work as it applies to assessment and treatment of persons with injury residual and/or functional limitations due to injury. The task of making determinations regarding impairment and

disability in persons with neurologic impairment and injury is fraught with potential obstacles and confounding issues. This is due in part to the frequently subtle yet complex nature of the deficits involved, as well as the lack of formal, scientifically validated "rating systems" for many of the deficits associated with these disorders. There are multiple possible types of problems associated with brain or other neurologic injury and there are often a number of other associated problems such as chronic pain or psychoemotional problems. Disentangling the multiple contributors to cognitive dysfunction and to impairment and disability presents a diagnostic challenge and requires careful scrutiny (1).

### IMPORTANCE OF RESPONSE BIAS IN BRAIN INJURY EXAMINATION

Persons with brain injury may present with some response bias to report or demonstrate impairment or related disability. Response bias, in this chapter, is defined as a class of behaviors that reflect less than fully truthful, accurate or valid symptom report and presentation. Importantly, response bias is a ubiquitous phenomenon affecting almost any domain of human self-report. Some forms of response bias may be associated with conscious manipulation or intent to deceive but many, or most, are not. However, in the context of impairment and disability evaluations, or



insurance related evaluations, the importance of conscious or other bias becomes more acute (2–4).

Given the frequent incentives to distort performance during impairment and disability examinations, assessment of examinee motivation to provide full effort to do well during assessment becomes a necessary component of such evaluations. The importance of detecting response biases is critical with regard to providing accurate diagnosis. Accurate diagnosis is prerequisite to provision of appropriate and timely treatment, to obtaining optimal recovery, to prevention of iatrogenic impairment and disability reinforcement, and to appropriate legal compensation decisions. The impairment / disability context and other internal or environmental variables make ensuring accurate representation of a patient's functional status essential. In order to ensure accuracy, a number of factors must be considered including decisions regarding validity of observed impairment and disability, symptomatology displayed during the examination, sensitivity and specificity of assessment measures, and generalizability of test findings to functioning in everyday life.

Blau (5) has expounded on the importance of determining response biases and measuring true levels of impairment in medicolegal situations. Essentially, in this arena, an alleged victim of a wrongful act or omission attempts to establish (a) causality to demonstrate entitlement to compensation for damages, which is awarded based on (b) level of damages suffered. In cases of less obvious, clear cut and significant trauma with psychological, neurologic or soft tissue damage, causality and level of current and future damages are more difficult to prove and expert evaluation and opinion is heavily relied upon for making legal determinations. In the parallel insurance situation, the insured attempts to access entitlements to health care treatment and disability benefits, and expert evaluation and opinion are relied upon for making policy determinations. In both cases, financial and other incentives clearly represent motivational factors that increase the likelihood of response bias in the form of exaggerated or feigned symptoms.

## RESPONSE BIAS ASSESSMENT

### Examinee Response Biases

Examinee response bias can take several forms. Bias ranges from symptoms that may be minimized to those that are exaggerated or feigned. Exaggeration or accentuation of symptoms is usually associated with other psychological factors such as catastrophizing and are less often associated with conscious deception for the purposes of obtaining financial or other compensation, i.e., feigning or malingering. Symptoms may be accurately or inaccurately attributed to different events. For instance, pre-existing symptoms may suddenly be attributed to an

accident, or pre-existing problems previously not noticed can suddenly be given more prominence due to attention and anxiety. Similarly, an accident may cause an aging person to do a self-inventory of health that reveals age related symptoms that were previously minimized or ignored. As awareness of these symptoms or difficulties, many of which may well be "normal" or common in the general population, are temporally related to an accident or injury, they are frequently misattributed to such an event. In addition, social realities also exert influence over response to injury and symptoms. For example, the vastly different consequences for diagnoses of cancer versus mild traumatic brain injury (MTBI) or back injury produce differential reinforcement. The former is clearly undesirable, negative and highly stressful, while the latter can result in desirable consequences (e.g., monetary compensation, avoidance of stressful work demands).

Martelli, Zasler, Mancini and MacMillan (6) reviewed the literature and found several injury context variables associated with poorer post-injury adaptation and recovery and increased likelihood of response bias. These are listed in Table 64-1.

These variables represent vulnerability factors, which can reduce effective coping with post injury impairments and increase the likelihood of maladaptive coping and response bias. They are not mutually exclusive and, as with the variables presented below, more than one can contribute to symptom report and presentation.

Additional review of the literature (7–15), combined with clinical experience, indicate several other sources of poor post-injury adaptation and increased likelihood of significant response bias that may be encountered during examinations. These are included in Table 64-2.

A frequently overlooked form of bias is that which is iatrogenic to an increasingly restrictive insurance and adversarial medicolegal system. In an effort to elucidate expectancy influences and bias for persons who have sustained injuries, Martelli and colleagues (6, 36) conducted convenience attitudinal surveys of professionals who evaluate and treat injured workers, rehabilitation and worker's compensation (WC) case managers, and injured workers. They found an overall 25% estimate of exaggerating or malingering WC patients, with highest estimates from WC case managers (29%), suggesting a general skepticism and distrust faced by injured workers. Furthermore, the majority of professionals and case managers filling out the survey believed that they would personally be treated unfairly by the WC system if they were injured, suggesting an even stronger general skepticism and distrust of the extant systems that fund evaluation and treatment of injury and disability. Although these data are preliminary, the findings are characteristic of the levels of diffuse distrust often observed by the authors in impairment and disability evaluation situations across the United States and Canada. These findings highlight the

**TABLE 64-1**  
***Variables Associated with Poor Post-Injury Adaptation and Response Bias***

<ul style="list-style-type: none"> <li>• Anger, resentment, or perceived mistreatment</li> <li>• Fear of failure or rejection (e.g. damaged goods; fear of being fired after injury)</li> <li>• Loss of self-confidence and self-efficacy associated with residual impairments</li> <li>• External (health, pain) locus of control</li> <li>• Irrational fear of injury extension, re-injury, or pain</li> <li>• Discrepancies between personality / coping style and injury consequences (e.g., highly physically active person with few intellectual resources who has a back injury)</li> <li>• Insufficient residual coping resources and skills</li> <li>• Prolonged inactivity resulting in disuse atrophy</li> <li>• Greater reinforcement for “illness” vs. “wellness” behavior</li> </ul>	<ul style="list-style-type: none"> <li>• Fear of losing disability status, benefits, and safety net</li> <li>• Perceptions of high compensability for injury</li> <li>• Pre-injury job (task, work environment) dissatisfaction</li> <li>• Collateral injuries (especially if “silent”)</li> <li>• Inadequate and inaccurate medical information</li> <li>• Misdiagnosis, late diagnosis, or delays in instituting treatment</li> <li>• Insurance resistance to authorizing treatment or delays in paying bills</li> <li>• Retention of an attorney</li> </ul>
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importance of considering the motivational factors that operate on examinees that present for impairment and disability evaluations.

In an interesting conceptualization of a major type of response bias in chronically disabled workers, Matheson (7, 10–12) defined symptom magnification as a conscious or unconscious self destructive and socially reinforced pattern of behavior or symptom production intended to control life circumstances of the sufferer, but which impede health care efforts. He further defined three major subtypes. The Type I “refugee” displays illness behavior that provides escape or avoidance of life situations perceived as unsolvable. Somatization, conversion, psychogenic pain, and hypochondriacal disorders are conceptualized as extreme subcategories for this type. The Type II “game player” employs symptoms for positive gain. Although this type seems associated with malingering, Matheson argues that true malingering is a medicolegal concept, while the Type II symptom magnifier is a treatable self-destructive syndrome. The Type III “identified patient” is motivated by maintenance of the patient role as a means of life survival. Associated psychiatric diagnoses include factitious disorder.

Main and Spanswick (15) examined the response bias of simulated or exaggerated incapacity in persons claiming physical disability. They identified a list of features associated with and suggestive of simulated or exaggerated incapacity associated with chronic pain. These include: failure to comply with reasonable treatment; report of severe pain with no associated psychological effects; marked inconsistencies in effects of pain on general activities; poor work record; previous litigation. Features that they found to be not primarily suggestive of response bias included: mismatch between physical findings and reported symptoms; report of severe or

continuous pain; anger; poor response to treatment; behavioral signs / symptoms.

### **Attribution and Bias**

Several sources of attribution bias which require assessment during evaluation of physical, sensory and neurocognitive impairments need to be considered.

*Examinee* attribution biases can confound accurate diagnosis. Examples include mistaking physical, cognitive, and motivation problems associated with depression and sleep disturbance for neurologic injury or sequelae. This can occur due to misattribution, over-attribution, retrospective attribution, illusory correlation, or to heightened awareness due to vigilance biases. Importantly, the previously mentioned conditions (e.g., depression, sleep disturbance) are reversible and may have been present prior to the injury without producing significant limitations. Furthermore, the emotional states or fatigue may be interacting with actual physical injury symptoms to increase impairment.

*Examiner* misattribution can similarly occur. Only methodical neurologic, psychologic and other assessment can differentiate sequelae secondary to brain injury from factors with overlapping presentations such as cranial/cranial adnexal and cervical trauma impairments, chronic pain, motivational factors and/or other psychological sequelae or other non-neurologic factors. When “abnormal” neurocognitive findings and/or non-specific somatic complaints are obtained, tendencies toward “over-diagnosis” of neurologic disorders, such as MTBI, can only be avoided through careful differential diagnosis. Brain injury specialists sensitized to neurologic symptoms have

**TABLE 64-2**  
***Additional Variables Associated with Poor Post Injury Adaptation and/or Response Bias***

*Cultural Differences.* For example, different cultures mix emotional and physical pain and symptoms at a conceptual and phenomenological level in different ways. Also, some cultures see failure to impose severe penalty / extract significant compensation for harm as a sign of weakness and disgrace in God's eyes.

*Conditioned Avoidance Pain Related Disability (CAPRD).* CAPRD represents phobic reactions associated with fear of pain wherein behavior, either gross motor activity (kinesiophobia) or cognitive exertion (cogniphobia), is avoided due to fear of exacerbation of pain. Such behavioral reactions are typically beyond or minimally within the realm of conscious awareness and control.

*Desperation Induced Malingering/ Symptom Exaggeration.* Individuals that are particularly prone to these types of response bias may include the following: insecure immigrant workers, immigrants who attempt cultural assimilation but feel resentful that they were not rewarded, aging workers, tired workers, workers insecure about work changes, workers fearing their own limited or declining abilities, persons whose premorbid coping was tenuous and who feel too overwhelmed and unable to cope with an additional stress, those with real or imagined abuse from others, such as employers, family, etc., immigrants who feel rejected by the culture and feel entitled, immigrants who feel disillusioned because the new land was not everything they had hoped (i.e., those who believe this to be a viable solution to a desperate situation). A second group of patients represented by this category are those making desperate pleas for help and those who, upon confronting tests that seem different and maybe easier than the real life situations where they have problems, reduce effort to highlight their problems. Again, in some individuals such responses may not be within conscious awareness or control but, in others, there may be more explicit and conscious attempts at deception.

*Sociopathic, Manipulative and Opportunistic personality traits.* These personality traits can be found in all groups, but may be associated with a greater incidence of conscious dissimulation.

*Passive Aggressive, Impatient, or Rebellious personality traits.* Such individuals tend to resent others for not listening to them and believing them. They tend to resent imposed evaluations or doctor's visits, especially ones that examine psychological function or motivation. They may play games with doctors by withholding or undermining procedures or treatments, and may alter performance on tests that seem non-challenging or do not appear face valid.

*Factitious and Somatoform Disorders.* Individuals with factitious disorder and somatoform disorders (i.e., conversion disorders including non-epileptic seizures [pseudo-seizures], somatoform pain disorder, somatization disorder, and undifferentiated somatoform disorder) may present symptoms that represent a combination of several items in this table or other factors.

*Psychological Decompensation.* These individuals usually display conspicuous psychological distress and pathology that differentiates them from others.

*Skepticism.* Many individuals are very skeptical of doctors, examinations and examination procedures, and may be poorly motivated to comply with the conditions required for valid assessment.

*Diagnosis Threat.* This refers to the effect of negative expectations on cognitive test performance. Suhr and Gustad (13, 14) demonstrated that subjects with a history of mild head injury performed significantly worse on general intellectual and memory measures, and rated themselves as putting forth less effortful performance, when attention was called to their head injury ("diagnosis threat"). This effect may play an important role in many situations where response bias and poor adaptation are noted.

*Iatrogenic bias.* A frequently overlooked form of bias is that which is iatrogenic to the nature of the insurance and adversarial legal system. Preliminary attitudinal data gathered from injured workers and the individuals who treat and case manage them (6, 36) indicates a strong and prevalent skepticism and distrust faced by injured persons in the extant insurance systems. This real or perceived mistrust reflects fear and expected unfair treatment from doctor's and insurance companies that can result in a deliberate and reactive magnification of symptoms. Persons most vulnerable to this type of bias may be persons or groups with tendencies toward suspiciousness, including immigrants, outcasts, outsiders, and those who feel chronically underprivileged, "slighted" or "short-changed". As indicate above, the increased attention called to head injuries can undoubtedly produce a "diagnosis threat" effect.

been observed by the authors to often misdiagnose chronic pain sequelae as post-concussive symptoms, which may result in an escalation of medical costs, prolongation of inappropriate treatment, and eventual treatment failure which may contribute to a sense of helplessness and

chronic disability in the injured person. Conversely, similar observations have been made for psychiatrists and psychologists prone to infer psychiatric or psychological etiologies for all pathology, including brain injury or actual physical injury (1, 6, 16).

## Response Bias Assessment

Formal response bias assessment procedures, which may be lacking or only haphazardly attended to in clinical examinations, must be employed in order to increase the probability that clinical examination findings are accurate and valid reflections of impairment. Response bias exists on a continuum that extends through denial and unawareness of impairments, symptom minimization, no bias to symptom magnification and malingering. While many examinees approach testing in a forthright and adequately motivated manner, it is necessary to examine the potential for response bias with each patient.

*Anosognosia* or unawareness of one's deficits is a neurologic phenomenon owing to dysfunction of brain operations subserving awareness (6, 16). This condition is usually more pronounced early after injury, is typically associated with more significant neurologic insults, and can lead to chronic under appreciation of deficits.

*Symptom minimization*, in contrast, may be a consciously or unconsciously motivated phenomenon. It is usually motivated by either a desire to engage in activities that might otherwise be restricted or to maintain a positive view of oneself and one's life (e.g., persons high in trait "social desirability"). *Denial* is a psychological defense employed unconsciously to protect one from facing painful realizations about losses that may be overwhelming and threaten the integrity of the self. Failure to detect such biases can result in failure to identify important impairments and an overestimation of abilities that could potentially endanger the welfare of the examinee.

*Symptom magnification*, in contrast, refers to accentuation or exaggeration of impairment. This can occur in relation to multiple factors, can represent an attempt to inflate financial compensation, and can serve a wide range of psychological needs. Some examples include efforts to legitimize latent dependency needs; resolve pre-existing life conflicts; retaliate against employer or spouse or other; reduce anxiety; fulfill self-denigrating or self-abasement personality patterns; exert a "plea for help"; or solicit acknowledgment of perceived difficulties. Symptom exaggeration can also occur in patients with pre-morbid histories of psychiatric and psychoemotional problems who "latch on" to a specific diagnosis which not only becomes responsible for all life problems, but also promotes passivity, helplessness, and an external locus of control. When patients are assessed for claims of major disability following uncomplicated mild and often even more significant brain injury, non-neurologic contributors should be closely scrutinized. Depression, post traumatic stress disorder and other anxiety conditions or other psychiatric syndromes or psychological processes such as catastrophizing can produce symptoms that are mistaken for neurologic impairment.

Misdiagnosis of these conditions serves to promulgate misperceptions and amplify functional disability and health care costs.

*Malingering* is deliberate symptom production for purposes of secondary gain, especially financial compensation. Malingering in the examination setting will often be associated with unexpectedly poor performance (6). Measures of response bias should always be administered regardless of the context of the evaluation. However, this should be considered imperative in cases of medicolegal presentation or suspicion of any incentive to make less than fully effortful or accurate presentation.

Importantly, the identification of unambiguous cases of malingering is difficult. Whereas the most convincing evidence of certain or definite malingering is a confession or admission, this seldom occurs and may not be truthful. A secondary form of evidence, also unreliable, is when the person or examinee is detected, via surveillance, performing an act that they reported that they could not do. Many persons will sometimes report being unable to do certain things which may represent a response bias to report problems, negative self-evaluations or poor self-judgment. A third form of evidence comes from corroboratory report, i.e., third party contradiction of what the examinee claims. There are also various problems associated with this evidence as is true of many situations when there is a discrepancy between what one party and another reports. Finally, a variety of instruments and examination procedures are available as indicators of response bias. Any of several measures designed to assess atypical, worse than chance performance, or non-organic responses can be employed to assess response bias in cognitive, motor, sensory or physical performances or self report. However, again, most of these measures also require careful clinical interpretation as there may be a number of possible alternative explanations for performance. *Importantly, the presence of response bias, although required, is not sufficient evidence of malingering as this is a probabilistic evaluation predicated on converging evidence from a thorough analysis and integration of history, contextual information, behavioral observation, interview data, examination and test data, collaborative data, and personality and emotional status data. It requires thoughtful analysis of all data (e.g., consideration of both secondary gain and secondary losses), as well as competent differential diagnosis to consider alternative explanations* (16). It also requires cautious and critical consideration of the probability of malingering vis-à-vis the limitations of the assessment and response bias measures and the potential consequences of incorrect impressions. *Measures of response bias provide valuable information for estimating the degree to which a person was presenting accurately, exerting full effort and the degree to which test results are reliable and valid and reflect actual*



*abilities. They do not provide reliable evidence of malingering.*

Evaluating clinicians should be familiar with psychological syndromes that may present as organic disorders, including factitious disorder and somatoform disorders (e.g., conversion disorders including non-epileptic seizures [pseudo-seizures], somatoform pain disorder, somatization disorder, and undifferentiated somatoform disorder), which may be important in the differential diagnosis of malingering. Of course, the presence of a psychological syndrome and/or response bias does not necessarily exclude the diagnosis of an actual neurological syndrome or malingering. This certainly complicates the process of disentangling multiple clinical entities that sometimes co-exist. Unfortunately, the art and science of methodical differential diagnosis is too often under-appreciated in the evaluation process (1).

### Examination Strategies

Physicians should be familiar with examination strategies designed to evaluate non-organic musculoskeletal and neurologic disorders, including the use of specialized bedside examination techniques for physical and cognitive dissimulation. Examples include such strategies as Hoover's test for evaluation of malingered lower extremity weakness, sideways/backwards walking for assessment of feigned gait disturbance, and a positive Stenger's test on audiologic assessment for non-organic hearing loss. Other tests that might be of value in the context of response bias detection on the physical examination include: Mankopf's maneuver, strength reflex test, arm and/or wrist drop test, hip adductor test, axial loading test, Gordon-Welberry toe test, Bowlus and Currier test, Burns bench test, Magnuson's test, and others (1, 17).

Examination findings that suggest a possible non-neurological basis for the observed impairments include patchy sensory loss, pain in an improbable nondermatomal distribution (such as a midline sensory demarcation), non-pronator drift, and/or astasia-abasia (18). Motor and other impairment inconsistencies that fluctuate or disappear under hypnosis, drug assisted interviews, or "presumed" non-observation may also suggest some psychophysiological or functional substrate and cast doubt on a hard-wired or intractable organic deficit. Importantly, some non-organic or non-neurologic signs such as hemisensory loss may be in response to central psychophysiological factors associated with actual changes in brain function (19). Both feigned and conversional hemiparesis are typically more common on the left side (18–20), perhaps due to the fact that most persons are right hand dominant. Consistency regarding laterality of symptoms, particularly with neurologic impairment and/or referred pain, should be evaluated.

When of central (versus peripheral) origin, pain complaints should be assessed, in part, by concurrently assessing temperature perception, given that the same neural pathways mediate these sensations. When temperature sensation is preserved in the presence of a loss of pain sensation, after either brain or spinal cord injury, the deficit is not likely to reflect direct CNS impairment (the loss should occur contralateral to and below the level of the lesion). This point also reinforces the need to understand the neuropathology/pathology of the lesion based on imaging studies and to appreciate the implications that these findings have for anticipated clinical exam findings. Alleged pain imperception can be evaluated, as can nearly any reported neurological impairment for that matter, with appropriately designed forced choice testing (21). Additionally, examiners should realize that alleged pain imperception or loss of sensation is difficult to fake upon repeated bilateral stimulation. This is due to the fact that examinees that exaggerate rely on subjective strategies rather than truly responding to the strength of the stimuli. Therefore, assessments with such techniques as Von Frey hairs could be utilized in the aforementioned scenario to provide further objective evidence of the validity of reported symptoms.

Defining pain and its possible deception is extremely challenging. The standard accepted definition of pain describes it as a physiologic and psychologic response to noxious stimuli, the latter being defined as a stimulus that may or does produce tissue damage (22). One must, however, differentiate between psychic and physical pain, or pain and suffering, in the context of performing an Independent Medical Evaluation (IME). These may be inextricably intertwined with each other as well as with affective conditions such as depression and anxiety. Examiners must understand that multiple variables may impact on pain reporting and behavior and be totally valid yet potentially appear invalid. For example, arousal, stress, tension and anger all may exacerbate subjective reporting of pain and pain behavior, as may depression, through psychophysiological effects. Psychoemotional and psychosocial concomitants of chronic pain must be appreciated, including loss of self-esteem, lowered frustration tolerance, depression, sexual dysfunction, including decreased libido, anger, and guilt.

A very recently disproved screening procedure frequently used by physical therapists, physicians, and chiropractors for estimating when psychological factors are significantly influencing pain related responses is the assessment for Waddell's Non Organic signs (23, 24). These signs include: Overreaction (guarding/limping, bracing, rubbing affected area, grimacing, sighing); Tenderness (widespread sensitivity to light touch of superficial tissue); Axial Loading (light pressure to skull of standing patient should not significantly increase low back symptoms); Rotation (back pain reported when shoulders and pelvis are passively rotated in the same plane); Straight Leg

Raising (marked difference between leg raising in the supine and seated position); Motor and Sensory (giving way or cog wheeling to motor testing or regional sensory loss in a stocking or non dermatomal distribution, when peripheral nerve dysfunction has been ruled out). Additional non-organic signs that have been considered have included: lower extremity give-away, no pain-free spells in the past year, intolerance of treatments, and emergency admissions to hospital with back trouble (15, 20, 23).

Initially thought to indicate degree of non-organic or psychological contribution to pain experience, the Waddell signs were never intended to exclude physical components as a cause of low back pain, or imply that psychological factors were a cause versus result of pain. More recent evidence indicates that the Waddell signs are not valid measures of non-organicity. In a structured, evidence based review of all available evidence, Fishbain (24) concludes that Waddell signs are neither correlated with psychological distress or secondary gain and do not discriminate organic from nonorganic problems. In fact, they may represent an organic phenomenon and are associated with greater pain levels and poorer treatment outcomes.

This finding has significant implications. By demonstrating the invalidity of one of the most heavily relied upon methods for making inferences and medical diagnostic conclusions about nonorganicity, it calls into question the general diagnostic validity of many physical and medical evaluations. Moreover, it almost certainly limits the utility of all commonly used psychological measures that were developed to predict medical diagnoses that relied on these invalid measures.

With regard to assessment of psychological and neuropsychological impairments and chronic pain, response bias represents an especially important threat to validity. As these assessments usually begin with an interview about self-reported symptoms and subsequently rely heavily on standardized measures of performance on well-normed tests, the validity of the results requires the veracity, cooperation, and motivation of the patient. Recent evidence, however, suggests that some patients seen for presumptive brain injury-related impairments over-report pre-injury functional status (25). This may be especially true with post-concussive deficits since these symptoms appear with similar frequency in the general population (26). In addition, the demonstrated ability of neuropsychologists to accurately detect malingering in test protocols has been less than impressive (e.g., 27). Finally, the common practice of utilizing technicians to administer tests, as previously noted, has been called into question for reasons that include adequacy to detect and manage response bias issues (28). Nonetheless, various instruments, techniques and strategies are available which have demonstrated at least some utility in detecting response bias, as a means of increasing confidence in the validity of assessment findings.

In Table 64-3, what have often been considered as hallmarks signs of response bias are presented (29). The signs can be applied to most aspects of a medical examination. However, as noted, caveats exist for most.

Notably, in the evaluation of response bias, as in evaluation of all aspects of pre- and post-injury status, the following investigative tools may be used in conjunction with client interviews and testing: 1) school records; 2) medical records; 3) driver records; 4) military records 5) criminal records; 6) employment records; 7) evaluations from other psychologists; 8) interviews with family members, friends, teachers and employers, etc.; and 9) all materials available to the attorney through formal discovery or otherwise.

These guidelines and strategies are presented as important possible indicators for interpreting patient examination data. Integration of contextual information, history, behavioral observation, interview data, collaborative data, and personality data, with measures of effort and neuropsychological test data provides the best information for estimating the degree to which a person was exerting full effort and the degree to which test results are reliable and valid and reflect actual abilities.

The recent increase in attention to response bias assessment and malingering may reflect a pendulum like overcompensation to earlier times when such issues were not properly appreciated and when excessive compensation packages or awards may have been made due to an assessment of disability that did not take into account response bias. In the current and increasingly restrictive healthcare environment, where services and benefits are more critically evaluated, and where legal and decision making policies favor either-or and black or white conceptualizations, there are tendencies to consider response bias as dichotomous and to consider response bias and malingering as synonymous. In fact, response bias measures are often erroneously referred to in many publications as "malingering measures". This undoubtedly contributes to what the authors note as too frequently haphazard and overzealous application of poorly validated detection procedures, failure to critically and objectively evaluate both the weaknesses, as well as strengths, of these procedures, and tendencies to overinterpret or overgeneralize them.

Again, it is especially important to realize that response bias and malingering are not synonymous. For example, Moore and Donders (30) showed that psychiatric history and financial compensation seeking were associated with a similar increase in likelihood of invalid responding on cognitive symptom validity and neuropsychological measures. Grillo, Brown, Hilsabeck, Price and Lees-Haley (31), using several indicators of response bias that included the Fake Bad Scale (FBS), offered evidence that characterologic / personality

**TABLE 64-3**  
**Response Bias: Typical Hallmark Signs**

**I. Inconsistencies Within and Between:**

1. Reported Symptoms
2. Examination / Test Performance
3. Clinical Presentation
4. Known Diagnostic Patterns
5. Observed Behavior (in another setting)
6. Reported Symptoms & Exam / Test Performance
7. Measures of Similar Abilities (inter-test scatter)
8. Similar Tasks or Items Within the Same Exam or Test (intra test scatter) - especially when difficult tasks are performed more easily than easy ones
9. Different Testing Sessions

*Caveat: The potential contributions of significant psychiatric, attentional, comprehension, or other problems that often involve inconsistent presentations should be considered in evaluating inconsistency.*

**II. Overly Impaired Performance (vs. expected)**

1. Very Poor Performance on Easy Tasks Presented as Difficult
2. Failing Tasks That All But those with Severe Impairment Perform Easily
3. Poorer Performance than Normative Data For Similar Injury/Illness.
4. Below Chance Level Performance

*Caveat: Unusually poor level of performance may be due to actual interference effects associated with various psychologic, sleep or other disturbances; statistically significant levels of below chance performance may be expected in 1/20 cases with the usual significance levels.*

**III. Lack of Specific Diagnostic Signs of Impairment**

*Caveat: Many disorders do not have unambiguous diagnostic signs.*

**IV. Specific Signs of Response Bias on Psychological or Neuropsychological Tests**

1. MMPI-2 Scales: F, F-K, L, VRIN, TRIN, Fb
2. MMPI-2 "Fake Bad Scale" (FBS) (103)
3. Malingering Detection Tests
4. Actuarial formulas for clinical neuropsychological tests (e.g., WCST, CVLT)

*Caveat: Many of these signs are not unambiguous or have not been thoroughly validated.*

**V. Interview Evidence**

1. Atypical temporal relationship of symptoms to injury
2. Psychological symptoms, or symptoms which are improbable, absurd, overly specific or of unusual frequency or severity (e.g., triple vision)
3. Disparate examinee history or complaints across interviews or examiners
4. Disparate corroboratory interview data versus examinee report

*Caveat: Other explanations are possible for disparate or atypical interview data.*

**VI. Physical Exam Findings**

1. Non-organic sensory findings
2. Non-organic motor findings
3. Pseudoneurologic findings in the absence of anticipated associated pathologic findings
4. Inconsistent exam findings
5. Failure on physical exam procedures designed to specifically assess malingering

*Caveat: As indicated above, non-organic sensory findings may have a psychophysiological basis as may psychogenic movement disorders or other pseudoneurologic presentations.*

disorder factors, rather than "malingering" contributes to exaggerated results in a forensic setting. Ample other evidence indicates that psychiatric or functional disorders can produce response bias or actual performance deficits

related to poor adaptation and maladaptive coping versus malingering (e.g., 32–35). There is also evidence that negative expectancy (e.g., "diagnosis threat"), independent of impairment, can reduce cognitive performance (13, 14).

Based on a critical evaluation of the current state of the art, it appears necessary to caution that malingering: 1) should not be considered dichotomous, as *either / or* (i.e., present or not present, black or white); 2) should not be considered something that clinicians can reliably or validly assess or diagnose with a high degree of probability, even when serious efforts are made; and 3) should not be considered a discrete entity assessed by often used response bias measures. Further, it should not be assumed that response bias measures have a high degree of reliability and validity in predicting valid examination performance on other measures or functional ability in other settings, or that patients take the examination process as seriously as examiners do.

A summary of some of the major limitations and problems with current response bias procedures include (8, 9, 19, 36–40):

- Psychometric research Inadequacies (i.e., basic test construction issues such as reliability and validity; sensitivity and specificity).
- Limited generalizability of analogue research (e.g., unknown differences between simulated and real malingerers).
- Variable Group Membership (wide variability in samples for both simulators and symptom disorder groups).
- Differential Vulnerability to Response Bias (some tests are more obvious or subtle, sensitive or specific).
- Questionable Generalizability of Findings (e.g., from analogue simulation studies to real life situations, from one response bias measure to another, to other tests, to actual symptoms, or across time).
- Absence of Mutual Exclusivity (poor effort can occur in presence of real disorders).
- “Law of the Instrument” bias wherein “malingering” becomes what “malingering” tests measure. Specifically, the definitions of “effort”, and validation studies to examine the construct, are often lacking. Further “effort” cannot be assumed uniform for individuals, individuals within diagnostic groups or for nonlitigating and litigating situations.
- Questionable Specificity: The effects of fatigue, pain, disinterest, non-attended (e.g., computer) administration, mixing cognitive tests and SVT’s in a battery with unknown validity, and other factors on response bias tests, are not understood and have not been addressed.
- Frequently High Misclassification (i.e., false positive or false negative) rates, especially in the very few studies that examined ecological or real world validity (38, 39).
- Incautious use of most current SVT Indexes with regard to diagnosis and decision making may violate APA ethics and “APA Standards for Educational

and Psychological Tests”, given the aforementioned psychometric limitations.

These limitations emphasize: 1) caution with regard to over-interpretation of response bias procedures; and 2) the importance of employing multiple data sources and making thoughtful inferences only after integration of thorough historical information, interview, assessment, behavioral observations, collaborative interview and data sources, and so on.

In order to caution against simplistic and dichotomous conceptualizations with regard to diagnosis, the following table is presented. Notably, Table 64-4 represents just 64 of the possibilities with regard to injury-related presentations. The represented possibilities range from (a) persons with real, uncomplicated disorders with impairments on exam and in functional status and without exaggeration on either (but possible minimization or denial) to (b) persons with complicated, misattributed or non-existent disorders with only exaggerated or feigned impairments on exam and/or in functional status. In an ongoing review of medicolegal report findings that will be submitted for future publication, the authors have examined the frequency of possible diagnostic conclusions in reports from cases in which they have been involved. Findings have consistently indicated that a preponderance of conclusions reflect only a few of these possibilities and reach mostly black or white diagnostic inferences regarding presence or absence of neurologic dysfunction and malingering.

A cautious approach is indicated with regard to estimating the probabilities regarding presence or absence of physical impairment and response bias. For instance, if a person has both actual symptoms and is exaggerating difficulty, inferences must be generated not only about the degree of deliberateness and the degree of physical impairment, but also the degree of awareness of

**TABLE 64-4**  
*Diagnostic Possibilities in Brain Injury Assessment*

BRAIN INJURY IMPAIRMENT	RESIDUAL FUNCTIONAL IMPAIRMENTS	RESIDUAL IMPAIRMENTS ON EXAMINATION
1. Yes	1. Yes & Exaggerated	1. Yes & Not Exaggerated
2. Mixed	2. Yes & Not Exaggerated	2. Yes & Exaggerated
3. Indeterminate	3. No & Exaggerated	3. No & Exaggerated
4. No	4. No & Not Exaggerated	4. No & Not Exaggerated



exaggeration on the part of the subject. Has the person adopted a sick role and talked themselves into believing they cannot perform certain tasks and lack certain abilities (e.g., somatoform disorder), with conscious withholding of effort due to intention of demonstrating what they believe to be true disabilities? Or, are they less conscious and aware, as in a conversion disorder? Or are they completely aware, but coping in a way that may be adaptive? An example of the latter is the case of an aging worker with a chronic history of back failures who has low self-esteem and a poor relationship with his or her employer. This employee may have a belief that another back injury is inevitable and will be cumulatively painful and disabling, will require uncomfortable interactions with others, may result in being fired despite conviction that the company did not make obvious safety precautions to prevent their injury, and that no other job options are realistic.

Table 64-5 presents a summary of major response bias detection strategies and techniques that may indicate that the validity of medical examination and psychological test data should be carefully considered. This table was prepared on the basis of a comprehensive review of existing literature (see 6–15, 17–21, 23–150). Multiple sources were used for most of the indicators. Special attention was given to reviews of specific empirical indicators such as those offered by Nies and Sweet (41) and Trueblood and Schmidt (57), which served as a model for this effort. Notably, this table illustrates the utility of a constellation or profiling approach to response bias detection. This multiaxial conceptual model is presented as a methodological approach for constructing a profile of motivation and response bias, which incorporates a wide array of findings from common instruments and procedures during evaluation. Empirical support exists indicating that each of these indicators has at least some utility in detecting sub-optimal effort or other response bias (e.g., 41, 45, 46).

Importantly, review of original test manuals and studies should be conducted before employing any of these instruments. Also, as noted previously, numerous pitfalls and limitations of each of these procedures, both conceptual and methodological, exist. However, some increasing evidence exists for improved discrimination and increased reliability when multiple measures are employed (54). The proposed conceptual approach is one in which multiple factors are integrated as an optimal method for estimating the degree of effort and the degree to which examination findings are reliable and valid. This conceptual model and procedure (MAP) for estimating motivation economically incorporates currently available instruments and methods and the available published research for direct and indirect measurement of effort and response bias. For review of these instruments and methods, the reader is referred to several good reviews

in textbooks of neuropsychology or the many previous reports and reviews of this literature (e.g., 9, 41, 45, 46, 54, 56, 104, 141, 148, 149).

Most major objective personality measures and many neuropsychological measures have scales or indices that can be calculated, (e.g., Memory Assessment Scales (60) and the Rey Complex Figure Test and Recognition Trial (61)) that provide data on the performance of simulators. The advantages inherent in such procedures include: reduced need for administering and charging for very long tests designed solely for detection of potential motivation problems (especially if negative), and for which numerous generalization difficulties exist; limiting the amount of available time for administering other relevant measures and conducting more comprehensive interview (examinee, collaborative others); potential enhancement of face validity of measures to examinees.

The techniques or strategies suggested in Table 64-5 should not be utilized singly or simple mindedly. They are not intended to support a simple dualistic model that equates response bias or other phenomena (e.g. actual interference effects associated with pain, psychoemotional distress, etc) to malingering and then considers examinee responses as either accurate or malingered. Evidence of response bias on any one test does not necessarily imply absence of impairment or in real world abilities. It cannot be concluded that failure on specific indicators represents inadequate performance or response bias. Rather, the strategies are offered with the following suggestions.

1. Examination responses can be influenced by multiple factors that affect the reliability and validity of examination presentations and performances (e.g., deliberate and nondeliberate effort, psychiatric disorders).
2. The degree to which presentations and performances displayed on examination accurately reflect genuine functional abilities exists on a continuum (versus a dichotomy) and can be estimated by the extent to which indicators of response bias are present.
3. Because the interpretation of findings and diagnostic impressions are dependent upon the reliability and validity of examination results, the reliability and validity of interpretations and impressions is reduced to the extent that indicators of response bias are present.

It should again be emphasized that “failure” on one measure of response bias does not mean that the entire set of complaints is biased or invalid. Ethical guidelines caution against overzealous interpretation of limited test data and, in this regard, with erroneously considering response bias and malingering as synonymous or dichotomous, or neglecting how psychiatric or other factors affect response bias measures. At present, the authors are

**TABLE 64-5**  
**Motivation Assessment Profile—Brain Injury Evaluations (MAP-BI)**

**Performance Patterns on Existing Neuropsychological Tests**

Full Scale IQ	
Low (vs. expected, estimated, etc.)	
Digit Span (Floor Effect)	Age Scale Score < 5
Digit Span: Testing Limits with “Chunking”	Non-improvement with “chunking”
Arithmetic and Orientation scale Performance	“Near-miss” (Ganser errors)
WMS-R Malingering Index: Attention/ Concentration Index versus Memory Index	Attention-Concentration Index Score < General Memory Index(AC-GMI)
Paired Associate learning: Easy vs. Hard item Performance	Hard Items $\geq$ Easy Items
General Neuropsych Deficit Scale (35)	GNDS Score < 44
Speech Sounds Perception Test Performance	>17 errors (Poor)
Seashore Rhythm Test Performance	>8 errors (Poor)
Finger Tapping Test	Unusually low w/o gross motor deficit
Tactual Stimulation Performance	Errors bilaterally vs. laterally
Finger Tip Number Writing – Errors	>5
Finger Agnosia – Errors	>3
Grip Strength	Unusually low w/o gross motor deficit
Category Test Performance	Rare or “spike three” errors; Or > 1 Error on Trials I or II
Wisconsin Card Sorting Test Errors	Discrepant # Perseverative vs. # Category Errors
Recognition memory (RAVLT)	< 6
Recognition memory (CVLT)	< 13
List Learning Serial Order Effects	Abnormal patterns
Warrington Recognition Memory Test (RMT)	Score < 38 (RMW), < 26 (RMF)
Rey Complex Figure Recognition Trial	Atypical Recognition Errors ( $\geq 2$ ); Recognition Failure Errors
Word Stem Priming Task Performance	Poor or unusual performance

**Instruments to Specifically Evaluate Level of Cognitive Effort/Response Bias**

Symptom Validity Testing (SVT)	sig * < 50% chance level responding
Hiscock Forced Choice Procedure (HFCP)	sig < 50% chance level responding, <66 correct
Victoria Symptom Validity Test (VSVT)	sig < 50% chance level responding, <16 on easy and/or hard items
Portland Digit Recognition Test (PDRT)	sig < 50%, chance responding
21-Item Test	<5 on free recall, <3 on free recall, <13 on recognition, <9 on recognition
Test of Memory Malingering (TOMM)	<45 trial 2 or recognition
Forced Choice test of Nonverbal Ability (61)	sig < 50% chance level responding
Dot Counting Test (DCT)	Correct/incorrect responses
Computer Assessment of Response Bias (CARB),	< 89% raises suspicion
Word Memory Test (WMT) IR, DR, Consistency	<89% raises suspicion
Autobiographical Interview (36)	>3 errors
Memorization of 16 Items Test (MSIT)	>8 Omissions, >6 Omissions, <6 Total Correct
Rey Word Recognition List (WRL)	<6 correct, <5 (total correct minus false positives)
Rey Memory for 15 Items Test (MFIT)	<3 complete sets, <9 items (38))
Word Completion Memory Test (WCMT)	R < 9 or Inclusion <15

\*sig = statistically significantly

**Personality Instruments with Built-in Detection Designs**

- Personality Assessment Inventory (PAI) (104)
- Inconsistency (INC), Infrequency (INF), Positive Impression Management (PIM), and Negative Impression Management (NIM) scales.
  - 8 score patterns thought to comprise a “Malingering Index”.
  - >2 patterns malingering suspected
  - >4 patterns likely malingering

TABLE 64-5 (continued)

Minnesota Multiphasic Personality Inventory (MMPI-2)	<ul style="list-style-type: none"> <li>• Validity indices (L, F, Fb, Fp, Ds, K, VRIN, TRIN, F-K) (44, 103, 105)</li> <li>• The Fake Bad Scale (105)</li> </ul> <p>Rogers (37) – cutoff scores:  <i>Liberal:</i></p> <ol style="list-style-type: none"> <li>1. F-Scale raw score &gt; 23</li> <li>2. F-Scale T-Score &gt; 81</li> <li>3. F-K Index &gt; 10</li> <li>4. Obvious – subtle score &gt; 83</li> <li>5. Conservative:</li> <li>6. F-scale raw &gt; 30</li> </ol>
<i>F-K index &gt; 25</i>	
<b>Qualitative Variables in Assessing Response Bias</b>	
Time /Response Latency Comparisons Across Similar Tasks	
Inconsistencies across tasks	
Performance on Easy Tasks Presented as Hard	Low scores or unusual errors
Remote Memory Report	Difficulties, especially if < recent memory, or severely impaired in absence of gross amnesia
Personal Information	Very poor personal information in absence of gross amnesia
Comparison Between Test Performance & Behavioral Observations	Discrepancies
Inconsistencies in History and/or Complaints, Performance Comparisons for Inconsistencies Within Testing Session (Quantitative & Qualitative):	Inconsistencies across time, interviewer, etc.
	A. Within Tasks (e.g., Easy vs. Hard Items)
	B. Between Tasks (e.g., Easy vs. Hard)
	C. Across Repetitions of same/parallel tasks (R/O fatigue)
	D. Across similar tasks under different motivational sets
Comparisons Across Testing Sessions (Qualitative, Quantitative)	Poorer/inconsistent performance on re-testing
Symptom Self Report: Complaints	High frequency of complaints; patient complaints > significant others'
<b>Main &amp; Spanswick Indicators (15)</b>	
<ul style="list-style-type: none"> <li>• Failure to comply with reasonable treatment</li> <li>• Report of severe pain with no associated psychological effects</li> <li>• Marked inconsistencies in effects of pain on general activities</li> <li>• Poor work record and history of persistent awards</li> <li>• Previous litigation</li> </ul>	
Symptom Self Report: Early vs. Late Symptom Complaint	
Early Symptoms reported late	
<b>Neuromedical Indicators</b>	
Hoover's test	Test for feigned lower extremity weakness associated with normal crossed hip extensor response
Astasia abasia	"Drunken type" non-organic gait with near-falls but no actual falls to ground
Non-organic sensory impairments	Patchy sensory loss, midline sensory loss, large scotoma in visual field, tunnel vision (Note: usually not, but sometimes, organic)
Non-neurologic upper extremity drift	Long tract involvement results in pronator type drift. Proximal shoulder girdle weakness and malingering typically present with non-pronator drift.
Stenger's Test	Test for malingered hearing loss during audiologic evaluation.
Gait discrepancies when observed versus not observed	If organic should be consistent regardless of whether observed or not.
Gait discrepancies relative to direction of requested ambulation	Gait should present with same impairments in all directions. Malingerers do not as a rule practice a feigned gait in all directions.
Forearm pronation, hand clasping and forearm supination test for digit/finger sensory loss	Malingered finger sensory loss is difficult to maintain in this perceptually confusing, intertwined hand/finger position

TABLE 64-5 (continued)

Pain versus temperature discrepancies	Due to the fact that both sensory modalities run in the spinothalamic tract, they should be found to be commensurately impaired contralateral to the side of the CNS lesion.
Lack of atrophy in a chronically paretic/paralytic limb	Lack of atrophy in a paralyzed/paretic limb suggests the limb is being used or is getting regular electrical stimulation to maintain mass.
Impairment diminishes under influence of sodium amytal, hypnosis or lack of observation	All these observations are most consistent with non-organic presentations including consideration of malingering or conversion disorder.
Incongruence between neuroanatomical imaging and neurologic examination	Lack of any static imaging findings on brain CT or MRI in the presence of a dense motor or sensory deficit suggests non-organicity.
Arm drop test	An aware patient malingering profound alteration in consciousness or significant arm paresis will not let their own hand, when held over their head, drop onto their face.
Presence of ipsilateral findings when implied neuroanatomy would dictate contralateral findings	An examinee claiming severe right brain damage who claims right eye blindness and right-sided weakness and sensory loss.
Tell me "when I'm not touching" responses	An examinee with claimed sensory loss who endorses that he does not feel you touch him when you ask him to tell you "if you do not feel this".
Lack of shoe wear in presence of gait disturbance	An examinee with claimed longer term gait deviation due to orthopedic or neurologic causes should demonstrate commensurate wear on shoes (if worn with any frequency)
Calluses on hands in "totally disabled" examinee	An examinee who is unable to work should not present with signs of ongoing evidence of physical labor
Assistive device "wear and tear" signs	In any examinee using assistive devices for any period of time e.g. cane, crutches, there should be commensurate wear on the device consistent with their claimed impairment and disability.
Mankopf's maneuver	Increase in heart rate commensurate with nociceptive stimulation during exam (there is some controversy on whether this always occurs).
Lack of atrophy in a limb that is claimed to be significantly impaired	If side to side measurements and/or inspection do not bear out atrophy consider other causes aside from one being claimed.
Sudden motor give-away or ratchitiness on manual strength testing	Considered to normally be a sign of incomplete effort or symptom exaggeration.
Weakness on manual muscle testing without commensurate asymmetry of DTRs or muscle bulk.	Suggests simulated muscle weakness if longstanding.
Toe test for simulated low back pain	Flexion of hip and knee with movement only of toes should not produce an increase in low back pain.
Magnuson's test	Have examinee point to area several times over period of examination; inconsistencies suggest increased potential for non-organicity.
Delayed response sign	Pain reaction temporally delayed relative to application of perceived nociceptive stimulus.
Wrist drop test	In an examinee with claimed wrist extensor loss, have them pronate forearm, extend elbow and flex shoulder . . . if on making a fist in this position they also extend wrist then non-organicity should be suspected.
Object drop test	Examinee claims inability to bend down yet does so to pick up a light object "inadvertently" dropped by examiner
Hip adductor test	Test for claimed paralysis of lower extremity, similar to Hoover's test yet looks for crossed adductor response
Disparity between tested range of motion and observed range of motion of any joint	When ROM under testing is significantly disparate (e.g. less) from observed, spontaneous ROM suspect functional contributors
Straight leg raise (SLR) disparities dependent on examinee positioning	Differences in SLR between sitting, standing and/or bending may suggest a functional overlay to low back complaints
Grip strength testing via Dynamometer	<ul style="list-style-type: none"> <li>• Three repetitions at any given setting should not vary more than 20% and/or</li> <li>• Bell shaped curve should be generated if all 5 positions are tested.</li> </ul>
<ul style="list-style-type: none"> <li>• 3 Repetitions</li> <li>• 5 Positions</li> </ul>	

TABLE 64-5 (continued)

Sensory "flip" test	Sensory findings should be the same if testing upper extremity in supination or pronation or lower extremity in internal versus external rotation. Differences may suggest a functional overlay.
Pinch test for low back pain	Pinching the lumbar fat pad should not reproduce pain due to axial structure involvement; if test is positive suspect a functional overlay.

**Important Considerations****Caveats:**

1. *The potential contributions of significant psychiatric, attentional, comprehension, or other disorders that often involve inconsistent presentations should be considered in evaluating inconsistency.*
2. *Unusually poor level of performance may be due to actual interference effects associated with various psychological, sleep or other disturbances, especially heightened anxiety or fear of pain.*
3. *Many disorders do not have unambiguous diagnostic signs*
4. *Many of these indicators are not unambiguous and have not been thoroughly validated.*
5. *Non-organic sensory findings may have a psychophysiological basis as may psychogenic movement disorders or other pseudoneurologic presentations.*
6. *Other explanations are possible for disparate or atypical interview data.*

preparing a paper that documents a group of severe TBI clinical subjects who are not in litigation or receiving compensation where large numbers "fail" response bias measures (i.e., score below recommended cut offs) despite very strong external reinforcement for performing well. In addition, several other researchers have submitted or are preparing papers that demonstrate similar results and/or document a proportion of subjects who fail response bias tests but perform adequately on neuropsychological measures.

A practical approach to considering the numerous indicators of response discussed in this chapter is presented in the flow chart in Figure 64-1. This flowchart is intended to facilitate the integration of these measures in deriving meaningful inferences regarding the presence and extent of response bias. This in turn serves the ultimate purpose of estimating the effect of response biases on performance and impairments noted on self report and examination.

Practitioners should recognize that a great disparity exists between the adversarial legal process where attorneys are advocates for their clients and the IME setting where the doctor must be dispassionate and objective. The danger of attorney "coaching" based on utilization of this material cannot be underestimated. This, of course, would then represent a form of "stealth" threat to the validity of examination data. This threat, or expected consequence of collision between the disparate legal and scientific ethics, has been documented in a publication noting a case of attorney client coaching (146). However, compared to simpler models where only a couple of isolated response bias measures are used, it seems more unlikely that the multiple measures employed in the MAP approach could be understood and manipulated.

Finally, enhancing response bias detection as a means of optimizing interpretability of examination results, critical as it is, should not be considered the final step. Decreasing the potential for response bias is a more efficacious and economic approach to enhancing utility of assessment. The following recommendations for enhancing motivation, assessing response bias, and increasing efficiency, utility and ecological validity of examination procedures are offered.

**RECENT DEVELOPMENTS**

Recent efforts to identify response bias and malingering have been problematic. Malingering, or the act of willful, deliberate, and fraudulent feigning, or gross exaggeration, is only one variant of response bias, and an extreme one. The presence of response bias is much more easily documented than malingering. However, the two are often confounded and used synonymously in professional neuropsychological publications and practice, where response bias measures are frequently referred to, explicitly or implicitly, as "malingering tests". Inferences about malingering, especially in a restrictive health care environment with strong gate keeping pressures, are inherently challenging. In the absence of dependent measures or clinical methods with demonstrated validity for assessment of malingering, inferences about malingering using current measures and procedures necessarily produce fallible judgments with unknown false positive rates.

Two of the major obstacles to developing highly reliability and valid measures of malingering are: the absence of an accepted gold standard, which accounts for the absence of any blinded studies comparing malingerers



Flowchart for Reponse Bias Assessment

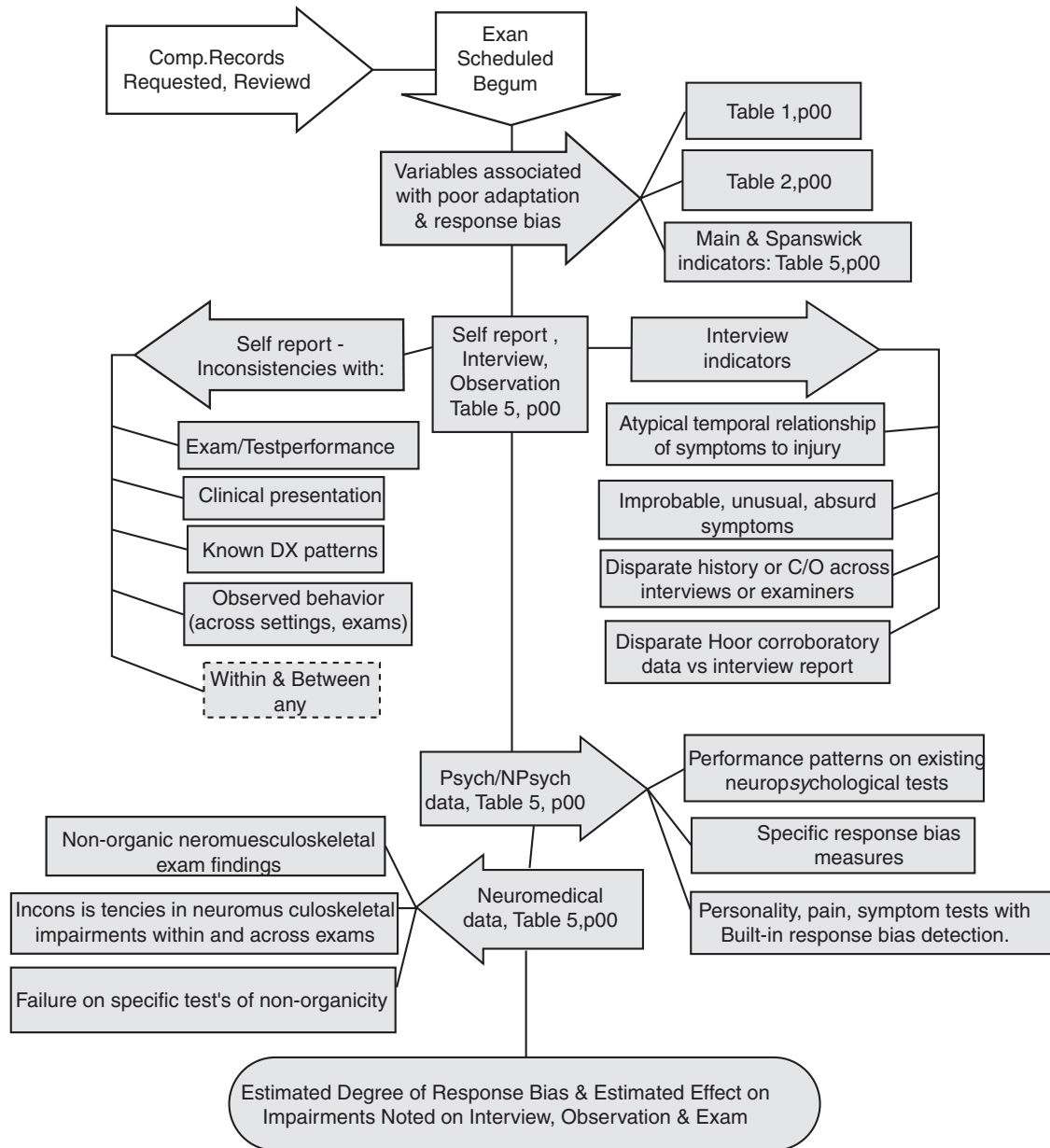


FIGURE 64-1

Flow chart for response bias assessment

and non malingerers; 2) nearly exclusive reliance on simulation studies (i.e., non-injured persons instructed to feign deficits) for establishing reliability and validity (129). In one of the only large group studies that examined the validity of symptom validity instruments for identifying cognitive malingering, the results suggested high false positive rates (38). A research design which attempts to circumvent obstacles relating to simulation studies and absence of a valid gold standard criterion for malingering is one that attempts to employ known

groups. That is, this design examines criterion groups of patients and purported or assumed malingerers and systematically analyzes differences between the groups. This approach may benefit from recent proposals for specifying criteria for malingering (129).

Drawing on previous research, Slick, Sherman and Iverson (151) have proposed diagnostic criteria for malingered neurocognitive dysfunction (MND), defined as volitional exaggeration or fabrication of cognitive dysfunction for the purpose of secondary environmental gain

(e.g., compensation or avoidance). The Slick et al. criteria allow for estimations of three probabilities of MND, including:

- **Definite MND:** presence of (1) substantial external incentive, (2) definite negative response bias on neuropsychological testing, and (3) definite negative response bias is not fully accounted for by psychiatric, neurological or developmental factors.
- **Probable MND:** presence of: (1) substantial external incentive; 2) evidence from neuropsychological testing, excluding definite negative response bias, and one or more types of evidence from self-report, and (3) information or data utilized for criterion #2 are not fully accounted for by psychiatric, neurological or developmental factors.
- **Possible MND:** presence of (1) substantial external incentive; 2) evidence from self-report; 3) information or data utilized for criterion #2 are not fully accountable by psychiatric, neurological, or developmental factors.

Slick et al. (151) urge that inferences regarding malingering be preceded by thorough consideration of differential diagnostic considerations of other types of response bias and psychological, neurologic and developmental contributors, and adoption of a “reasonable doubt” strategy that considers the limitations of assessment methodology, and the cost of false positive errors.

The Slick et al. Proposed Diagnostic criteria for malingering are helpful in delineating the need for multiple indicators for poor effort, and consideration of other, non-SVT factors to be considered in reaching a somewhat less dichotomous diagnosis of definite, probable or possible malingered neurocognitive deficit. However, they nonetheless still suffer from a somewhat limited consideration of factors that can contribute to poor symptom validity test scores, as well as all of the previously noted limitations of available symptom validity measures. Regarding the latter, Ranks (152) recently examined a series of individual cases using detailed analysis of symptom validity measures with the best currently available research support. His presentations, which are being prepared in a manuscript, demonstrate the problems of symptom validity assessment in individual cases using instruments that appear much stronger when examining data from group studies. In findings from a recent investigation by Loring, Lee and Meador (153), the Victoria Symptom Validity Test (VSVT) was found to identify cases of incomplete effort in patients being evaluated for strictly clinical purposes in which no external incentive to perform poorly has been identified. It was also noted that the older patients appeared to be at increased risk for suboptimal performance. Gorissen, Sanz and Schmand (154) investigated schizophrenia patients and

reported that suboptimal performances on symptom validity tests reflected core components of that psychopathology. This suggests that effort is a component of many neurologic disorders and false positives can be expected on tests of effort and motivation, especially in the case of executive impairments.

Evidence from these and other studies (e.g., 152–154) indicate that true base rates for effort test scores (for which there may be a wide range of possible base rates for an individual) have not been established, and that at least some norms from samples that have been offered are unlikely to be representative. Hence, statements from test authors that anyone who is not severely demented can pass such tests appear overly exuberant or misleadingly presumptuous. The search for simple solutions has a long and illustrious history in psychology and medicine where initially positive signs or tests are widely and prematurely and incautiously adopted. Examples such as using the MMPI “conversion V” (58) or the Waddell nonorganic physical signs (23) to purportedly discriminate organic from nonorganic physical etiologies, represent just two examples. In both cases, the professions have shown slow and recalcitrant willingness to abandon these false safety blankets after proving to be invalid indicators. This has been despite the immense potential for negative consequences, and in seeming disregard for core bioethical principles that dictate nonmaleficence (i.e., “First do no harm”).

Sreenivasan, Kirkish and Garrick (155) have recently offered an interesting practical model for the assessment of amplified neuropsychological and psychiatric deficits in civil litigants in cases of MTBI. They proposed a more comprehensive and detailed checklist intended to assist with differentiating between subtle brain dysfunction, symptom amplification, psychological causes for the presence of cognitive and other deficits, or frank malingering. The checklist included examination and rating of patterns for greater consistency with either genuine injury or symptom exaggeration in the following areas:

- I. Neuropsychological testing issues, including: (a) base rates for brain injury, (b) testing consistency with severity of injury and (c) findings on motivational tests;
- II. Congruence of testing data and observed behavior during testing (within and between) with: (a) CNS process; (b) across serial testing; (c) with medical reports; and (d) with occupational and/or school functioning;
- III. Congruence of symptoms or signs with clinical data, including consistency of symptoms/signs with clinical interview (within and between) with: (a) clinical course; (b) past records; (c) physical exam; (d) objective laboratory and test findings; (e) collateral or surveillance data; (f) medication response for natural

history of CNS disease; (g) social, occupational, and/or school functioning;

- IV. Nonclinical factors, including: whether there is: (a) decline in income/business versus pre-injury; (b) pending pre-injury lawsuits; (c) pre-injury work related burn out, job actions, co-worker conflicts and skills problems (d) compensation less than pre-injury income; (e) repeated evaluations with same tests; (f) evaluation context impacting presentation; (g) reasonableness of expectations for recovery;

In addition, it allows for evaluation of the presence or absence of:

- V. Psychiatric and other conditions that may contribute to amplified or atypical symptoms, including: (a) depression/anxiety; (b) personality disorder; (c) conversion/somatization; (d) substance abuse; (e) cumulative concussion; (f) impact of chronic pain; (g) impact of medications; (h) impact of medical comorbidities
- VI. Miscellaneous history, including: (a) prior history of litigation; (b) prior history of lying, malingering; (c) prior criminal activity; (d) prior job track record; (e) prior responses to injury

This model appears to warrant closer consideration, especially with regard to its attention to differential diagnosis and specification of the alternative contributors to failure on symptom validity measures. Future efforts to identify factors predictive of response bias and symptom invalidity should also pay more attention to not only indicators suggesting response bias, but also ones that are inconsistent with response bias and secondary gain, including secondary losses.

### **Recommendations for Enhancing Validity in Impairment and Disability Assessment Findings**

1. Establish rapport and a basic working relationship with patients and examinees. Even in cases of independent evaluations where the referral source and expectation is adversarial, valid data collection requires a collaborative effort. The possibility of dissimulation might be reduced given better rapport (9, 130, 131), understanding of reported symptoms or complaints and communication of that understanding, as well as explanation, feedback and clarification given any suggestion of uncertain motivation. Spend time with patients and try to get to know them as individual persons. We cannot assume that everyone takes our exams and procedures seriously, is as honest or effortful as we would like, or that we will not have to work at getting them interested or invested in doing their best.
2. Ensure that emotional variables affecting motivation are adequately assessed during an interview that is conducted prior to the exam. Specifically, assess the impact of anger or blame and feelings of resentment or victimization (130, 131), as well as the other variables shown in the literature to be associated with poor recovery and adaptation to impairment (6). Assess pain, fatigue or other factors that may actually interfere with optimal performance. Always assess interest/ disinterest in the testing process and any obstacles or impediments to optimal effort and performance. Prepare patients / examinees before beginning testing. Employ understanding, as well as education to help prepare persons to perform to the best of their ability.
3. Make efforts to maximize validity of exam procedures. Where possible, utilize instruments with built-in symptom validity measures. Where possible, utilize comparisons with published patterns and indices indicating sub-optimal test performance for available tests for which there are data for symptom validity indicators (e.g., hand dynamometer; finger tapping; the Wechsler Memory Scale-Revised General Memory vs. Attention/ Concentration index). For example, in addition to comparison of three repeated trials at the same position and comparison of assessment at all five positions, repeat testing with the hand dynamometer allows analysis of consistency of performance patterns across time. Further, measurement of completion time for similar tasks also allows analysis of consistency. Additionally, validity indicators should be developed for existing assessment procedures and symptom validity measures should be built in to newly developed cognitive assessment tests and procedures. Finally, most measures of symptom validity have limitations and caution is advised. Efforts should be made to avoid making strong inferences from instruments for which there are not available data regarding sensitivity and specificity in clinical samples. Instruments with disputed or disproved validity (e.g., Waddell signs) should not be employed or given credibility.
4. Employ shorter symptom validity tests in order to minimize possibility of negative reactions owing to the nature of protracted participation in easy, boring, or atypical tasks. Where possible, employ procedures that both appear more credible and are not well-known. Vary measures and procedures that are employed in order to prevent discrimination of ability measures from symptom validity measures. Publicization of these tests has led to increased recognition by attorneys, clients, support groups, internet groups, and so on. Finally, do not freely share information about symptom validity measures to non-medical professionals. Other professionals adhere to a completely different set of professional



ethics and recent law publications indicate a practice of preparing clients for testing by counseling them with this information (125, 146).

5. Validity of examinations will likely be enhanced when conducted by clinicians who treat persons with brain injury, which also helps to assure more adequate clinical skills for detecting and modifying sub-optimal performance, as well as collection of internalized tracking data to allow validation of previous inferences across time. More experienced brain injury clinicians are more capable of: a) integrating history, interview, corroboratory interview / reports, collateral data, test findings, and personality and emotional status data with more sophisticated clinical observations during examination; (b) adapting more creative modifications of exam procedures and instructions given suspicion of low motivation, to increase motivation and optimize effort; (c) benefiting from the probability that examinees will be more forthcoming and more trusting of an experienced 'doctor'.
6. Remain aware that, in science and medicine, situations are rarely either-or, clear-cut, or one-dimensional. Avoid simplistic conceptual models that are compatible with dichotomous approaches to assessing effort and response bias. Such approaches usually rely on a couple of measures with cut off scores. Cut off scores, by their nature, always entail judgment (150), inherently result in misclassification and impose an artificial dichotomy on essentially continuous variables. "True" cut off scores do not exist. Employ sophisticated, continuous conceptualizations of effort and response bias by using multiple independent measures of estimated effort. Employ a model that conceptualizes motivation and effort as continuous variables that can vary across exam procedures, settings, and occasions. Performance data provides the best information for estimating the degree of effort exerted, and the degree to which test results are reliable and valid.
7. Utilize and devise models that measure the degree of apparent motivation and effort, using multiple data sources, and estimate confidence levels of inferences, given consideration of the multiple factors that contribute to exam findings. Employ similarly sophisticated models for assessing persistent impairments, adaptation to impairments, and disability. Probability statements based on multiple measures are the most appropriate. Integration of contextual information, history, behavioral observations, interview and collaborative data, personality and coping data with multiple measures of effort or performance and current tests exam and qualitative data provides the best information for estimating the degree of effort exerted, and the degree to which test results are reliable and valid.

## CONCLUSION

Evaluation of impairments following brain injury presents a significant challenge with numerous potential obstacles and confounding issues. In addition to frequently subtle but complex deficits, the lack of validated "rating systems" for many residual impairments, and the multiple contributors to impairment and disability, persons with brain injury may present with some bias to report or demonstrate impairment or related disability. Given frequent incentives to distort symptoms during examinations, assessment of examinee motivation is necessary to providing accurate diagnosis. This is prerequisite to provision of appropriate and timely treatment, promotion of optimal recovery, prevention of iatrogenic impairment and disability reinforcement, and appropriate legal compensation and treatment access decision making. In the current chapter, the importance of response bias was reviewed. Response bias assessment procedures relevant to brain injury assessment and treatment were considered and elucidated and appropriate cautions were indicated. Finally, recommendations for enhancing validity in impairment and disability evaluations were offered.

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# 65

## Decision-Making Capacity After TBI: Clinical Assessment and Ethical Implications

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**T**he ability to assess decision-making capacity is one of the “core competencies” of brain injury rehabilitation. Questions about the presence or absence of this capacity lie at the root of many of our recurring clinical and ethical dilemmas. The extent to which a patient can make health care decisions, decide to live without supervision, participate in research, enter into contracts or even engage in sexual activity depends on the nature and extent of their decisional capacity. Unfortunately, many brain injury clinicians feel uncomfortable and ill-prepared to evaluate these abilities. The situation is compounded by the fact that the standard bioethical model of decision-making capacity has limitations when applied to brain injury.

The result is that, “quite frequently”, inadequate attention is paid to assessing decision-making capacity or obtaining legitimate consent in brain injury rehabilitation (1). Even when attempts are made to assess decision-making capacity, there are significant discrepancies between the assessments made by rehabilitation clinicians and those performed by trained experts (2). These difficulties may partly account for the findings of a congressional investigation that brain injury rehabilitation centers often infringed on patients’ autonomy (3). Rehabilitation clinicians do recognize their shortcomings in this area and have ranked as amongst their highest priorities further

education on decision-making capacity as well as the patient’s role in decision making (4).

The objective of this chapter is to enable brain injury clinicians to assess the decision-making capacity of their patients as well as to understand the ethical implications of their findings. Although patients face many types of decisions after a brain injury, we will focus on the capacity to make health care decisions. It is in this realm that questions about decision-making capacity first arise after a brain injury. Moreover, we believe that the model for assessing the capacity to make health care decisions is, with some modification, directly transferable to other contexts (such as deciding to live without supervision, engaging in sexual activity, or entering into contractual relationships).

The chapter is arranged in sections as follows:

- Foundations: balancing autonomy and beneficence
- Decision-making capacity: key principles
- The standard model of assessing decision-making capacity
- Clinical application of the standard model
- The role of neuropsychological testing
- Limitations of the standard model in brain injury
- Choosing an alternate decision maker
- Beyond consent: assent and dissent
- Surrogate decision-making: the special case of withdrawal of care

## FOUNDATIONS: BALANCING AUTONOMY WITH BENEFICENCE

Although our society has long protected the right of individuals to make and act on their own decisions, Anglo-American medicine had been slow to honor this right or even the principle of autonomy underlying it (5). Now, however, autonomy is the foundational value in both bioethics and health care law. The practical consequence of our commitment to this ideal is that patients, and not family members or health care professionals, have the right to make the final decisions regarding their care.

The value of respecting a patient's autonomy is based partly on the presumption that the patient is in the best position to judge what is in her best interest. However, respecting a patient's wishes has value even when she chooses a course of action detrimental to her own welfare. That is, even if a person's choice is not in her best interest, the legal and ethical consensus is that her free exercise of will is more important than preventing any harm that may result to her from the choice made. Of course, the possibility that *others* may be harmed might justify overriding a patient's choice.

If autonomy is so valuable, why shouldn't we honor the choices of all our patients, including those with brain injuries? The answer has to do with the concept of competence. For a patient's choice to be counted as autonomous, and thereby respected, it must be the product of an adequate capacity to reason and choose. But it is precisely this capacity that can be impaired in people with brain injuries. Therefore, the determination as to whether or a not a person's choice is to be honored depends crucially on whether the person is competent to make that decision.

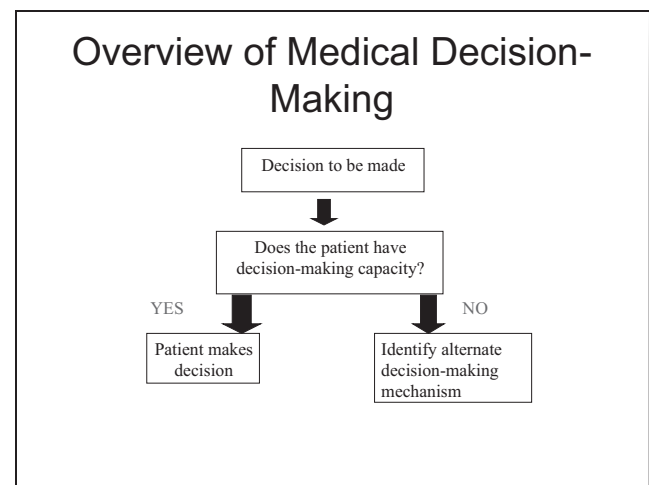
When a person is found to be competent, then the value of autonomy outweighs all other considerations. That is, it is only under extraordinary circumstances that we can override a patient's choice, no matter how much we believe it might harm them. On the other hand, if a person lacks decision-making capacity, then the value of beneficence, which represents a commitment to protecting and even enhancing a person's welfare, is paramount. Although we may still choose to honor the patient's wishes for other reasons, we can now offer a justification (the patient's welfare) for overriding their choices.

Thus, the concern with assessing decision-making capacity is motivated both by a concern with autonomy *and* a concern with beneficence. If a person is competent, we want to make sure that we do not infringe on their ethical and legal right to control their own life. On the other hand, if a person is incompetent, we are obligated to recognize this so that we can prevent or mitigate any harm that may come to them as a result of their choices. This is why it is so important that our assessment of a patient's decision-making capacity be accurate.

## DECISION-MAKING CAPACITY: KEY PRINCIPLES

Whenever a medical decision is to be made, the first step is to determine if the patient has the capacity to make that decision. (Figure 65-1) If so, the patient's wishes must ultimately be honored. If not, an alternate decision maker must be found. Most of this chapter focuses on how to assess whether a patient has decision-making capacity. Near the end however, we will discuss how to identify the appropriate decision maker when a patient is found to lack decision-making capacity.

The model of decision-making capacity that we present represents by far the most widely accepted account, both in bioethics and in the law (6). It should be noted, however, that there is some disagreement about the details of the model, even in the law, where different judicial opinions have occasionally relied on different theories of competence (7). In the text, we have indicated when there are alternatives to the views we present. We start by outlining some general principles which will frame the rest of our discussion. (Figure 65-2) First, it should be noted that, strictly speaking, "competency" is a *legal* category. This means that only a court can find someone incompetent in a particular area. The terms, "decision-making capacity" or "decisional capacity" are used to refer to the *same* set of abilities, as assessed clinically. Therefore, as clinicians, we assess the decision making capacities of our patients, not their competence. Although the legal system does rely heavily on assessments provided by clinicians, the ultimate determination is a judicial one. However, this does not mean that clinicians must rely on the courts every time there is a question about a person's capacity to make decisions; this would overwhelm the legal system. In the vast majority of cases, these assessments can and should be made by clinicians.



**FIGURE 65-1**

Overview of medical decision-making

1. Competency is a *legal* category; decision-making capacity is its clinical correlate.
2. Decision making is a *process*. Assess *how* the decision is made, *not what* is decided.
3. Evaluation should involve *direct observation* of a person's decision making abilities. Avoid inferring from the diagnosis or specific cognitive deficits.
4. Decision-making capacity is *domain specific*. One can be incompetent in some areas (e.g. financial management) but not others (e.g. medical decision making).
5. The decision making abilities required will *vary* with the demands of the situation. Consider how the patient's abilities match up with the demands of the particular decision to be made.
6. The more significant the consequences of a decision, the greater the evidence of competency required ("sliding scale" model).

FIGURE 65-2

## Fundamental principles of competency

Later in the chapter, we will discuss when recourse to the courts might be necessary. For now, the key point is that competence and incompetence are *legal* terms and are most appropriately used to describe judicial determinations. However, because it is common in everyday clinical situations to use the terms "competence" and "decision-making capacity" interchangeably, we will occasionally do the same. Readers should be aware of the distinction, however.

Another key principle is that the focus of an assessment should be on the process by which a decision is made rather than the decision itself. If the process by which a decision is made is sound, then the decision is considered valid, regardless of the clinician's opinion of its merit. Theoretically, the emphasis on the decision making process might lead to a situation in which a particular patient is determined to lack decision-making capacity even while another patient, making the same decision under identical circumstances, is considered competent. This would happen when the process by which one of the patients reached her decision was impaired, while the other's was satisfactory. Further detail on how to assess the decision making process in actual clinical situations will be provided in the next section.

The importance of evaluating the actual decision making process also means that one cannot infer the presence of decision-making capacity from a patient's diagnosis or cognitive deficits. Clearly not everyone with a brain injury or impaired memory lacks decision-making capacity. For this reason, we need to assess patients individually, in the context of the particular decision being made. Ideally, we should observe them as they engage in the process of making the decision that is at issue. This

way we can directly assess their ability to understand, appreciate, and reason with the relevant information (components of decisional capacity that we elaborate on below).

In addition, an assessment of decision-making capacity is distinct from an evaluation of cognitive capacities such as memory, attention, cognitive flexibility, etc. Although these processes affect or even underlie decision-making capacity, deficits in these areas do not automatically preclude the presence of decision-making capacity. Therefore, their evaluation should never supplant (although it can supplement) the direct observation of a person's decision making abilities. This issue will be discussed further in the section on the role of neuropsychological testing.

Decision-making capacity is rarely an all-or-nothing phenomenon; a person may lack the capacity to make certain decisions but not others. In other words, decision-making capacity is domain specific. This is also true of legal determinations of competency. For instance, someone may be found to be incompetent to manage her financial affairs but competent to make medical decisions. In the same way, a clinician may decide that a patient has the capacity to make decisions regarding her place of residence but not about whether to undergo a medical procedure.

Moreover, even *within* a domain, the decision-making capacity required will vary with the particular decision being made. This is because different decisions make different cognitive demands on the patient. Even with regard to medical decision making, patients may be able to make some decisions but not others. For instance, someone may be able to make a simple decision where the risks are low and the benefits high (for instance, to undergo surgery for acute appendicitis) but be unable to make a more complicated decision involving intermediate risks and different categories of outcomes (for instance, trading off a low risk of death for a moderate improvement in functional status). Thus, all assessments of decision-making capacity must be done in the context of the specific decision being made. This principle is well summarized by Grisso and Appelbaum, when they write that ". . . competence is not simply dependent on a person's abilities, but on the *match or mismatch between the patient's abilities and the decision-making demands of the situation that the patient faces.*" (From Ref. 6, p. 23)

Another corollary of the context dependence of assessing decision-making capacity is that the potential consequences of a decision should affect how thoroughly we investigate a patient's abilities. This is known as the "sliding scale" model of assessment. The idea is this: the more significant the consequences of a particular decision, the more evidence we should require that a person has decisional capacity. For example, we would require stronger evidence that a patient has decision-making capacity when she chooses to forgo life sustaining treatment than



when she refuses an antacid to treat gastric reflux. The greater the risk to the patient, the more we need to be certain that the decision represents an autonomous choice.

### THE STANDARD MODEL OF ASSESSING DECISION-MAKING CAPACITY

We have stressed the importance, in assessing decision-making capacity, of contextual features such as the nature, demands, and consequences of the decision being made. We now turn to the specific abilities that constitute decisional capacity. (Figure 65-3) Although the terminology used to describe these skills varies, there is agreement in the bioethical and legal literature about the nature of the abilities themselves. In what follows, we adopt the terminology used by Grisso and Appelbaum (6).

The first and most basic ability required is the ability to *express a choice*. A person who is not able to express (either verbally or behaviorally) a preference lacks decision-making capacity. This would certainly be the case early after a brain injury, before a patient has recovered consciousness. Even after patients have regained the ability to express preferences, however, it is important to recognize that the ability to express a choice is by itself insufficient to establish decision-making capacity. Patients must also possess the other abilities discussed below. The importance of expressing a choice lies in its absence, signaling unequivocal lack of the capacity to make decisions.

A second ability required in order to make decisions is the ability to *understand* relevant information. In the context of medical decision making, this information would include the nature and rationale of the treatment and its risks and benefits as well alternatives to the proposed treatment (as well as their risks and benefits). (Figure 65-4) Of course, this assumes that the clinician herself know what the risks and benefits are; there is considerable

1. The ability to *express a choice*
2. The ability to *understand* information relevant to treatment decision making
3. The ability to *appreciate* the significance of that information for one's own situation, especially concerning one's illness and the probable consequences of one's treatment options
4. The ability to *reason* with relevant information so as to engage in a logical process of weighing treatment options.

Adapted from *Assessing Competence to Consent to Treatment* by Grisso and Applebaum, 1998, Oxford University Press

**FIGURE 65-3**

Components of decision-making capacity

evidence that rehabilitation clinicians have difficulty in estimating patients' risks for activities such as walking, living alone, etc (8).

Of course, simply understanding the information is not enough; one must acknowledge that it is relevant to one's situation. We refer specifically to an *appreciation* of one's condition, with a special emphasis on how the intervention(s) being proposed applies to one's own circumstances. This ability is often impaired in people with brain injuries and manifests itself as decreased insight into any deficits that are present. As a result, a patient may evince complete understanding of the information outlined in Figure 65-4 and yet be unable to relate it meaningfully to her own situation.

In addition to understanding and appreciating the relevant information, patients must also be able to *reason* appropriately. The information must be processed by the patient in a logical and coherent manner. For one, a patient needs to relate the various possible outcomes to their own values. For example, is the value the patient places on physical independence reflected in their thinking and the choices they make? Patients also need to be able to imagine what the consequences of the various options would be. Ideally, patients would be able to go beyond simply verbalizing consequences to being able to describe the potential effects on their life (for instance, to appreciate the impact on their life of possible impotence after prostate surgery). These are just some of the factors that we all consider in making these sorts of decisions.

### CLINICAL APPLICATION OF THE STANDARD MODEL

How does one assess whether or not a person has the required abilities to choose, understand, appreciate and reason? While the evaluation of some of these abilities seems fairly straightforward (e.g. is a person capable of expressing a preference?), the assessment of others seems to be more complicated (e.g. how to assess reasoning ability?). In what follows, we offer suggestions on how clinicians can evaluate a patient's decisional capacity. Our

- Nature and rationale of treatment
- Risks and benefits of treatment (including their likelihood)
- Risks and benefits of the alternatives (including no treatment)

Adapted from *Assessing Competence to Consent to Treatment* by Grisso and Applebaum, 1998, Oxford University Press

**FIGURE 65-4**

Relevant information that patients must understand

focus throughout is on a “bedside” evaluation which can be performed without the aid of more formal tools. However, we should note that such tools are now being developed, including one developed by Grisso and Appelbaum (6). In addition, we address the role of neuropsychological testing in the next section.

As we mentioned earlier, one of the key principles of assessing decisional capacity is that we operationalize our assessment. This means that we should evaluate the abilities described above when a patient is actively involved in the process of making a decision. During this process, we can engage the patient through a series of questions. (Figure 65-5) The point is that we are not inferring the patient’s capacities from either their diagnosis or cognitive deficits (e.g. impaired memory); we are directly examining the abilities in question.

The questions outlined in Figure 65-5 for assessing appreciation, understanding, and expressing a choice are self explanatory. As we mentioned above, assessing the component of reasoning is the least straightforward. The strategy here is to ask the person to “think out loud”. That is, one asks them to retrace for the examiner the process by which they reached their decision. The examiner observes for a logical and coherent thought process. Of special interest are issues such as: how does the person understand and weigh risks (including their likelihood), is the person making a choice consistent with the values that they profess, is the person able to imagine the consequences of the various options, etc.

#### ABILITY TO EXPRESS A CHOICE

“Please tell me what your decision is.”

#### ABILITY TO UNDERSTAND THE RELEVANT INFORMATION

“Can you tell me, in your own words, what you know about:

- Your condition.
- The treatment recommended
- The risks and benefits of this treatment
- The risks and benefits of other options (including no treatment at all).”

#### ABILITY TO APPRECIATE ONE’S OWN SITUATION

“Can you tell me what you believe is wrong with you?”

“Do you believe that you need some sort of treatment?”

#### ABILITY TO REASON WITH THE RELEVANT INFORMATION

“Tell me how you reached your decision”

“What factors did you consider?”

Adapted from *Assessing Competence to Consent to Treatment* by Grisso and Appelbaum, 1998, Oxford University Press

The assessment of a patient’s decision-making capacity is not limited to an evaluation of their abilities to understand, appreciate, and reason. As discussed previously, the context in which these capacities are exercised is crucial. In particular, one needs to understand the specific decisional task the patient is confronting. This is because different tasks make different demands on understanding and reasoning. We should adjust the degree of understanding and reasoning we expect based on the inherent nature and complexity of the decision. For example, certain treatments in acute care medicine may result in a somewhat higher risk of death initially but a better functional outcome for survivors. These outcomes and the resulting necessity to balance values such as death and functional status make greater demands on understanding and reasoning abilities than, for instance, deciding to undergo a minimally risky treatment that should lead to a cure.

In addition to taking into account the complexity of the decision to be made, one should also keep in mind the possible consequences of the decision. This is because, the more significant the consequences, the more evidence of decision-making capacity we should require. For instance, if a patient refuses a low risk, potentially life saving intervention, we would require that they more thoroughly demonstrate evidence of their decision-making capacity than if they refused a high risk intervention with little chance of success. We should adjust the questions that we ask and the answers we deem acceptable based on the likely impact on the patient’s welfare.

Although we have stressed the indispensable role of direct observation of a person’s decision making abilities, there is a role for supplementary information. Specifically, in addition to the assessment outlined in Figure 65-5, one should also solicit information from third parties including caregivers and family members. As a result of the time that they spend with the patient, they often have a richer knowledge of the patient’s decision making abilities than can be gathered from the clinician’s formal assessment. For instance, their observations of how the patient reasons through other decisions or situations will have some bearing on how they deliberate in the present situation. More importantly, there are factors that may be relevant to decision-making capacity that may only be gleaned from direct observation of behavior in other realms.

For instance, as we will discuss below, it is entirely possible that a person could satisfactorily answer the questions asked in a formal assessment, and yet not behave in a way consistent with their answers. This “verbal-behavioral dissociation” is often seen in people with brain injuries but, by its very nature, can easily be missed in the verbally and cognitively biased assessment that we have outlined. Supplementary information in the form of observations by family members and other third parties is crucial in these cases. Of course, one must always

**FIGURE 65-5**

Questions to ask in assessing decision-making abilities

keep in mind the possibility of conflicts of interest between family members and the patient that might affect the information provided.

Finally, a few logistical points should be made about the assessment. First, because cognitive capacities can fluctuate after brain injury, multiple evaluations are often necessary to ensure that a person's best performance is observed. Performing such serial assessments also allows one to establish the consistency of a patient's choices over time. The absence of such consistency (for instance, when a patient changes her decision from day to day) raises serious questions about a patient's decision-making abilities. Moreover, one must also be mindful of any potentially reversible factors that might influence a person's ability to make decisions. Examples would include medication effects and the impact of fatigue. As much as possible, one should attempt to minimize the effects of such factors in the interests of maximizing a patient's performance.

It is also important to ensure that the optimal mode of communication has been established. Communication impairments are ubiquitous in brain injury, ranging from specifically linguistic problems (i.e. aphasia) to higher order impairments (e.g. pragmatic deficits). As a result, it is crucial that adequate communication exists such that there is little doubt that information is being appropriately conveyed to and from the patient. Also, adequate time needs to be spent with the patient to ensure that all the relevant information is provided and that all questions are addressed. Any ancillary means to enhance the disclosure of information should be utilized (e.g. written explanations, visual aids, augmentative communication, etc.).

### THE ROLE OF NEUROPSYCHOLOGICAL TESTING

Neuropsychological testing often plays a significant role in the evaluation of decision-making capacity. We believe, however, that its proper function can be misunderstood. In particular, we are concerned that testing can become a substitute for the direct clinical assessment of decisional capacity, resulting in less accurate and potentially inappropriate conclusions. Neuropsychological testing should play a *supplementary* role in the assessment of decisional capacity; the determination of intact or impaired decision-making capacity should rarely be based solely on the results of such an evaluation. We want to stress that our concerns are limited to *formal testing* only and not assessments performed by neuropsychologists. In fact, by virtue of their training and skills, neuropsychologists are ideally suited to perform the clinical assessment described earlier in the chapter.

It is easy to see why the formal assessment of cognitive deficits is thought to be central to the evaluation of decisional capacity. After all, impairments in decision-making

capacity are a direct result of the neuropsychological sequelae of brain injury. The cognitive, affective, and behavioral domains affected by brain injury form the substrate of most of our everyday tasks, including our ability to make decisions. Since discrete cognitive capacities such as attention, memory, language, etc. underlie the ability to make decisions, it seems only natural that these be formally assessed whenever decisional capacity is in question. However, the desire to base conclusions regarding decision-making capacity purely on formal testing is based on a misunderstanding of the nature of decision making abilities and the ways in which they are affected by cognitive deficits.

Although impairments in decision-making capacity are a *consequence* of neuropsychological deficits (whether cognitive, affective, or volitional), they are not identical with them. The ability to make decisions is best understood by analogy to other abilities in rehabilitation medicine, such as walking. In the case of walking, the inability to walk is the consequence of a complex interaction between various physical deficits (e.g., weakness in different muscle groups, spasticity, deconditioning, residual abilities in other parts of the body, presence of neglect, etc.) as well as the context in which one walks (e.g., level surfaces, carpet, incline, etc.). Although one could theoretically devise a model that incorporates all of these variables to predict whether a particular patient will walk, it is far easier to perform a direct assessment by standing them up and attempting to walk with them. Moreover, given the complexity of walking and its dependence on context, no model will ever be as accurate as direct assessment.

Similarly, the ability to make decisions is the consequence of a complex interaction between various mental capacities (memory, abstract reasoning, attention, etc.) and the context of the decision to be made (whom to vote for, whether to undergo surgery, to engage in sexual activity, etc.). Once again, given the number of variables involved and the complexity of their potential interaction, it would be far easier to directly assess decision-making capacity (as outlined earlier) than attempt to infer its presence or absence from what are, at best, surrogate markers. In addition, the importance of taking the context into account can not be over-emphasized: a particular cognitive deficit might impair the capacity to make one decision but not another.

Because decision-making capacity is not identical with the capacities that underlie it, there is no clear way to determine what pattern of test findings preclude adequate decision making. Even with isolated deficits, there is rarely a one to one correspondence between a deficit and the ability to make a particular decision, much less the ability to make all decisions. For instance, while it is clear that impaired attention can affect most of the components of decisional capacity mentioned above (for instance, understanding or reasoning), it is not clear, except in cases

of extreme impairment, what degree of attentional deficit precludes adequate decision making. We have to return to the direct assessment outlined above (Fig. 65-5) in order to confirm that a patient's inattention is significantly affecting their ability to process information.

The problem is compounded by the fact that, as mentioned above, decision making tasks of differing complexity require different levels of understanding or reasoning abilities. Therefore, a person with impaired attention may have the capacity to make a simple decision but not a more complex one. Once again, we would have to assess the person's abilities directly. Finally, because one can compensate for attentional deficits to a certain extent, the same degree of attentional impairment may result in a patient having decision-making capacity at some times and not others (depending on whether the information is presented in a quiet, distraction-free environment, repeated several times, etc.). There are cases described of patients believed to lack decision-making capacity solely because they had certain deficits on testing (e.g. aphasia), who were found, on a more direct assessment, to actually have decisional capacity (especially when compensatory strategies were employed) (9).

The inability to "read off" a person's decision making status from their cognitive impairments is the primary obstacle to relying *exclusively* on neuropsychological testing; however, there are other limitations as well. It is difficult to test certain capacities that have a direct bearing on decision-making capacity. The best known of these are the so called frontal lobe capacities such as cognitive flexibility, the ability to plan, the ability to consider hypothetical situations, etc. Frontal lobe function can only be incompletely tested at the present time and patients can do well on formal testing even though they have frontal lobe dysfunction directly affecting their decisional capacity (10, 11). This is not as much of an issue when one is directly assessing decision-making capacity because one is directly observing the effects of possible frontal lobe deficits on the patient's reasoning. That is, one can directly observe the patient's ability to consider consequences, recognize and weigh alternatives, assess the ability of a particular decision to realize their goals, etc., all in the context of the decision in question. Once again, direct assessment will usually be superior to a formal assessment of certain neuropsychological domains.

Indeed, we believe that the actual determination of a person's decision-making capacity can often be made independently of a formal neuropsychological evaluation. This is because, as we have outlined above, the components of decision-making capacity (evinced a choice, understanding, appreciation, and reasoning) can be *directly* assessed (Fig. 65-5), without having to evaluate the cognitive capacities that underlie these abilities. While it is true that cognitive functions such as attention or memory form the basis of decision-making capacity, it is *not*

necessary to know how and to what extent they are affected in order to determine whether or not a patient has adequate decision making abilities for a particular situation. Since we are primarily concerned with the *effects* of cognitive deficits on decision-making capacity, we would be better off assessing the decision making abilities directly, rather than inferring them from neuropsychological test results.

In fact, studies that have investigated the correlation between neuropsychological test results and decision-making capacity acknowledge that the clinical assessment of decision-making capacity is the "gold standard" (11, 12). The aim of these studies was to determine whether testing by itself could match the accuracy of direct clinical assessments. Not surprisingly, while neuropsychological test results were correlated with the presence or absence of decision-making capacity, testing by itself was never as accurate as direct clinical assessment (13-16).

Despite its limitations, formal testing does have an important role to play. There are at least two purposes it can serve. First, the presence of deficits on testing can alert us to the possibility that a patient's decision-making capacity may be impaired. For instance, the identification of a short-term memory problem, while not enough to determine that a person lacks decision-making capacity, can prompt a direct assessment to make that determination.

More importantly, neuropsychological testing allows us to determine *why* a person's decision-making capacity may be impaired. The "direct" assessment that we outlined earlier simply allows us to determine whether or not a person has decisional capacity adequate to the task at hand. It rarely allows an identification of the cognitive impairments that underlie a particular patient's difficulties. For example, a person's inability to understand the information provided by a clinician may be caused by inattention or a language deficit. While knowing the cause does not alter the determination that the person lacks decision-making capacity, it does allow the clinician to target interventions to either correct the underlying deficit (e.g. discontinuing a sedating medication) or compensate for it (e.g. provide verbal explanations for someone with alexia).

### LIMITATIONS OF THE PROPOSED MODEL IN BRAIN INJURY

If forced to choose one method of evaluation, the direct assessment of decisional capacity is superior to neuropsychological testing. However, the two approaches complement each other and are best used together. Unfortunately, even this combination is sometimes not enough, especially in the case of brain injury. This is primarily because both direct assessment as well as neuropsychological testing have a strong cognitive bias. That is, they

are heavily weighted towards evaluating the cognitive aspects of decision making while virtually ignoring the affective, volitional, and behavioral domains which are often impaired in people with brain injuries. As is well known, cognitive abilities can often dissociate from these other domains. As a result, someone whose cognitive functions are preserved may be thought to have adequate decision-making capacity when, in reality, deficits in emotion, volition, or behavior may be impairing their ability to make decisions.

The most obvious example is the person who is unable to conform their behavior to their professed beliefs and desires. There are many people with brain injuries who are able to reply appropriately to questions about how they would act in particular situations but are unable to do so when they are actually confronted with them (17). Unfortunately, an assessment that limits itself to purely verbal or written responses (such as in a clinical interview or formal testing) will not be able to identify these problems precisely because they arise only when the patient is performing an action. For instance, in assessing whether someone has the capacity to decide to live on their own, one would ask how the patient would respond to different scenarios (for instance, smelling a gas leak). Even if the patient responded appropriately, one can not automatically assume they will act in the way they described. This might be because they have difficulty with impulse control which circumvents their ability to act in ways they might have intended. Or, the patient may have an amotivational syndrome that affects their ability to act on any of their beliefs or desires. These examples underscore the point made earlier about the importance of supplementing interview-based data with behavioral information obtained both through one's own observations as well as those of others.

Despite its significance in many contexts, the dissociation between cognition and behavior is not quite as relevant for decisions regarding health care. This is because for these decisions the patient rarely has to act; rather, they are passive recipients of others' actions (as in undergoing surgery). Since there is rarely behavior on the patient's part following a health care decision, a cognitively oriented evaluation should be adequate. For those decisions that do have a prominent behavioral component (such as the decision to engage in sexual activity), such an evaluation would have to be supplemented by knowledge of a patients' behavior.

Information about verbal-behavioral dissociations is often relatively easy to collect. Unfortunately, there are other non-cognitive impairments that may be more difficult to detect, thus increasing the chances that someone might be thought to have decisional capacity when, in fact, they don't. The most common of these impairments involve disorders of affect such as moderate to severe depression. Although it is known that depression can

directly affect cognition (for instance, information processing efficiency, short term memory, etc.)(6), these effects should be detectable by a direct assessment such as the one outlined in this chapter (at least in so far as these deficits compromise decision making ability for the decision at hand).

However, disorders of affect can compromise decision making in more subtle, but still significant ways (7). For instance, depression can alter how one values certain outcomes. Consider a severely depressed patient who is faced with a potentially life saving intervention with relatively low risk and minimal discomfort. The patient may have full understanding of the intervention, an appreciation of her medical situation, and adequate reasoning or information processing skills. She may still choose to refuse the intervention because she no longer wishes to live and sees her condition as offering an opportunity to die (18, 19). According to our original model, one would consider this patient to have intact decision-making capacity because she has the requisite cognitive capacities that are the focus of the evaluation. What is impaired is her ability to *value* appropriately; her depression causes her to favor outcomes that she would not have favored prior to the onset of her mood disorder.

The impact of emotions on decision making extends beyond the classical disorders of affect, however. Brain injury can affect emotions in other ways, most notably in the form of the hypoemotionality that can be seen after ventromedial frontal lobe injury (20). According to Damasio, certain frontal lobe injuries can result in an impairment in ". . . assigning different values to different options, . . . [thereby making one's] decision-making landscape hopelessly flat." (from 20, p. 57) He elaborates: ". . . the process of emotion and feeling are indispensable for rationality. At their best, feelings point us in the proper direction, take us to the appropriate place in a decision-making space, where we may put the instruments of logic to good use." (from 20, p.58) In the case of depression, patients still have the capacity to value; however, their valuations are inappropriate and different from what they would have been in the past. In the case of hypoemotionality, however, the capacity to value *any* outcome is impaired, thereby compromising decisional capacity in the way outlined by Damasio.

Impairments of hypo-emotionality are often difficult to identify on standard neuropsychological assessments. Indeed, one patient that Damasio discusses did well on all neuropsychological tests, even those specific for frontal lobe dysfunction. Yet, this patient had profound deficits in making decisions in "real life" situations, attributed to his affective impairments (20). For similar reasons, the assessment of decision-making capacity that we have presented, focused as it is on cognitive skills such as understanding and reasoning, may also fail to identify these sorts of impairments.

Decision making not only involves the ability to value outcomes appropriately but also the ability to respond appropriately to risks. This goes beyond simply understanding the quantitative aspects of risk, which can be impaired in depression (21). It also involves the appropriate emotional reaction to risk (such as being averse to risk unless the potential benefits outweigh the risks involved). Unfortunately, brain injury can also distort risk taking behavior, potentially changing the decisions patients might otherwise have made. For instance, depression after a brain injury can cause people to become more risk averse (22). This might prevent a depressed patient from choosing a moderately risky but highly beneficial medical intervention which they might normally have chosen before they became depressed. Yet, the patient's ability to express a choice, understand, appreciate, and reason would be found to be intact, leading one to conclude that the patient's decision-making capacity was not compromised. Other disorders of affect may cause similar distortions of our perception and response to risks. For instance, anxiety may also cause a state of risk aversion while mania or hypomania can cause one to be risk seeking. Regardless of whether one becomes more or less risk averse, these classical disorders of emotion can affect decision making in a way that would be difficult to detect by either direct assessment or formal testing.

In cases of hypoemotionality, there is evidence that individuals may lose the ability to feel *any* emotional response to the presence of risk. For instance, studies have shown that many patients with frontal lobe injuries do not manifest the normal activation of the sympathetic nervous system when confronted by risk (20, 23). These patients subsequently demonstrated increased risk taking behavior (23). The implications for decision making are clear. In the case of behaviors, not having the appropriate emotional response in the presence of risk will probably lead to increased risk taking with implications for a person's capacity to decide to, for instance, engage in sexual activity. Even for decisions that don't necessarily lead to overt actions on the part of the patient (such as medical decision making), the lack of the affective component of risk perception may lead patients to decide on risky interventions that they might otherwise have avoided. Once again, purely cognitive evaluations such as direct clinical assessments or formal testing will be unable to detect the influence of this type of affective impairment on decision making.

These evaluations will also fail to identify other impairments in decision making that can occur after frontal lobe injury. For instance, there is evidence that patients with ventromedial injuries discount the future excessively and, as a consequence, distort their decision-making by placing undue weight on short term gains or losses at the expense of future gains or losses (23). In the context of medical decision making, this might lead to

a patient deciding against an intervention that might have some temporary discomfort early on but significant benefits in the long-term. Or the reverse might happen: the patient may choose an intervention that provides some short-term gains but may actually be deleterious in the future. It would be difficult to identify this sort of impairment through direct clinical assessment or testing. One would have to rely on behavioral evidence based on one's own observations or reports from others. Unfortunately, this evidence is often not available in the first few months after brain injury since patients have not yet been in contexts where they have had to make many of their own decisions. This type of temporal "myopia" can also affect behavior such that patients might choose short-term pleasure (e.g. not using contraception) over long-term risks (e.g. an unwanted pregnancy).

Finally, there is evidence that frontal lobe injury can result in a lack of sensitivity to behavioral reinforcers (24). This might lead someone to repeat poor decisions because the aversive consequences of that decision are limited in their ability to change the patient's behavior. This sort of deficit is more relevant to decisions involving actions (such as those involving sexual activity) than those that involve health care decisions. When assessing for the presence of this type of deficit, one can often rely on evidence of past behaviors.

In summary, there are a variety of affective or behavioral impairments that can directly affect decision making and yet not be detected by either direct assessment of decisional capacity or formal testing: lack of sensitivity to behavioral reinforcers, temporal myopia and changes in valuation and risk perception (whether caused by classical disorders of affect or hypoemotionality). Of these, only those deficits related to classical disorders of affect (such as depression, anxiety, and mania) are readily accessible to routine clinical examination (whether in the form of interview or formal questionnaires). One should supplement all evaluations of decision making with these assessments to probe for the presence of any significant affective symptomology. If present, more time will need to be spent determining the effects of these affective symptoms on valuation and risk perception. Unfortunately, it is more difficult to assess for the effects of hypoemotionality on valuation and risk perception, the presence of temporal myopia, or the lack of responsiveness to behavioral reinforcers. At the present time, other than finding clues from knowledge of past behaviors and the clinical interview, there is little guidance available on how to directly assess for these deficits.

Even after taking into account volitional, affective, and behavioral issues, there is another situation encountered after brain injury that challenges our traditional methods of assessing decision making. This situation arises when a moderate or severe brain injury seems to cause a fundamental change in the patient's identity.

Family members often comment on these types of changes by statements such as “She’s a different person”, “He’s not the man I married”, or “I’m living with a stranger”. This phenomenon has significant implications for the status of the decisions made by someone with a brain injury.

For instance, consider someone who seems to have full decision-making capacity as outlined above (i.e. no significant deficits in understanding, appreciation, reasoning, or expressing their choices) *and* no significant affective, volitional, or behavioral deficits. However, they now make decisions that they clearly would not have made prior to their injury. For example, what they value and consider important may have changed so that they now spend their money on activities that they would not have before their injury. These sorts of changes are undoubtedly part of the phenomenon that the family describes when they note that the patient is “a different person”. Moreover, families often see the patient’s new choices as *prima facie* evidence that the patient has lost decision-making capacity.

In these situations, the clinician is faced with a difficult situation: someone whose decision-making capacity appears to be intact but who is now choosing courses of action that she may not have chosen prior to the injury. Should the person’s decisions be honored? This is a controversial question which has been most extensively discussed in the context of dementia (25, 26). In someone with a brain injury, our belief is that, as long as the person currently has intact decision-making capacity, their decisions should always be honored. The patient who is being treated is the patient as they are *now*. We feel that it would be unfair to the patient as they are now to sacrifice their autonomy and interests for the sake of their former self.

Finally, although not unique to people with brain injuries, it is important to be aware of any psychodynamic issues that might be affecting a patient’s decision making. We have been struck by how often a person’s decision is determined not by the information at hand (e.g. the risks and benefits of the treatment and its alternatives, etc.) but rather by underlying psychological factors that may or may not be apparent to the patient. Unless explicitly addressed, the examiner will almost always miss the presence and significance of these factors. Yet, these psychological issues often represent the “missing piece of the puzzle” that makes sense of what might appear to be a perplexing decision. This is particularly true when there appears to be a “gap” between the patient’s apparently intact cognitive capacities and the seemingly “irrational” choice they make.

For instance, a young adult may refuse a relatively innocuous medication simply because her family also wants her to take it and she is trying to establish independence from them. Her decision is determined by the conflict with her family and *not* by the indications and

effects of the medication itself. However, the patient may articulate her refusal in terms of her fear of the side effects. Even when reassured about the side effects, she might still maintain her refusal, suggesting to the family and clinician that her decision-making capacity might be impaired. Or, a patient may be very anxious about her symptoms and demand that “everything be done” to evaluate the cause, despite reassurance by the clinician of the benign nature of her condition. Further exploration might reveal that the patient had a family member who became very ill or died after developing similar symptoms.

In both cases, a direct assessment of decisional capacity may fail to reveal any significant deficits. Rather than simply acquiesce, however, clinicians should spend time exploring psychodynamic issues when faced with these dissociations between intact decision-making capacity and seemingly irrational decisions. Recognition of these psychological factors provides an opportunity to address what is really motivating the decision and, hopefully, result in a situation where patients base their decision solely on information that is directly relevant to the treatment.

#### WHEN SOMEONE LACKS DECISION-MAKING CAPACITY: CHOOSING AN ALTERNATE DECISION-MAKER

When it is determined that a patient lacks decision-making capacity for a particular decision, we must rely on alternate methods of making that decision. (Figure 65-1) Most states specify an order which must be followed in identifying another mechanism of decision making. (Figure 65-6) Assuming that the patient does not currently have a guardian, it is important to establish whether or not the patient has retained the capacity to execute a durable power of attorney for health care (DPAHC, which may go by different names in other states). As discussed in further detail below, such a document allows patients to designate another person to make health care decisions for them. Although it might seem odd that a patient who is considered incapacitated from making medical decisions might still retain the capacity to appoint

- Current guardian
- Establish if patient has the capacity to execute a DPAHC
- Advance directive
- Surrogate decision maker (designated by state statute)
- Appoint guardian

**FIGURE 65-6**

Example of alternate healthcare decision-making (Texas) listed in order of priority

a surrogate decision maker, this is clearly in line with the emphasis placed earlier on the context specific nature of decision-making capacity.

What is required to execute a DPAHC is that a patient must *appreciate* why they need someone to make decisions for them, *understand* the nature, benefits, and risks of a DPAHC, its alternatives, and of the person they might designate, and *reason* with this information in a logical and coherent manner. There are patients who either understand or accept that they are unable to make medical decisions and who have strong feelings about who they want to be making decisions in their stead. As long as these patients understand the nature and implications of a DPAHC and alternatives and have logical and appropriate reasons for preferring a particular person, they should be allowed to designate a surrogate decision maker by executing a DPAHC. In fact, in our experience, courts have favored this approach since it represents the “least restrictive” limitation of a patient’s autonomy.

If a patient does not currently have the capacity to execute a DPAHC, one should ascertain whether they had executed one prior to their injury. This would represent one type of an advance directive, known as a proxy directive. The other type of advance directive is known as a decision directive (6, 26). In contrast to the proxy directive, a decision directive does not identify a surrogate decision maker. Rather, it specifies what decisions a patient would want made under particular circumstances. For instance, a person may specify in advance that they do not want to be placed on a ventilator if terminally ill. Thus, a decision directive attempts to anticipate possible scenarios and outlines patients’ wishes should they be unable to express them. The familiar “living will” is one example of a decision directive.

Although very useful in some situations, decision directives have limited applicability in the context of brain injury. The primary reason for this is that very few people have executed advance directives of this sort, especially in the age groups often affected. Even when they exist, decision directives rarely address the situations most often encountered in the rehabilitation setting; rather, they almost always focus on terminal illness. It is true that some states recognize decision directives that apply in cases of permanent unconsciousness or severe disability; however, even these will only apply to a subset of the patients encountered in most rehabilitation settings (26).

More useful in brain injury rehabilitation are proxy directives. Rather than attempt to anticipate the myriad decisions that need to be made, these types of advance directives allow a person to designate a proxy to serve as the decision-maker. As discussed earlier, the Durable Power of Attorney for Health Care (DPAHC) is the legally recognized method for designating a health care proxy. The advantage of such a proxy directive is that it allows the designated decision-maker to make all healthcare

decisions that the patient could have made, unless limited by the patient in the directive. Unfortunately, as with decision directives, proxy advance directives are rarely available in the context of brain injury rehabilitation.

The decision-maker designated by a proxy directive is one example of a surrogate decision-maker. A surrogate decision-maker is one who is morally and/or legally empowered to speak on behalf of another person. In the case of a proxy directive, the surrogate’s authority derives from the fact that the patient explicitly designated them as the proxy. However, there are other methods of choosing a surrogate decision-maker, should the patient not have specified someone in advance. These include a person recognized through state surrogate statutes or a court appointed guardian.

The vast majority of patients do not have either a guardian or an advance directive. To address this situation, many states have adopted statutes that specify, in order of priority, who should serve as the surrogate decision-maker for an incapacitated patient. While the order may vary slightly depending on the individual state statute, the hierarchy usually formalizes the conventionally recognized “next of kin” as the decision-maker. For example, a spouse would precede the adult child, who would precede the parent, who would precede siblings, etc. If no family exists, then even a close friend or clergyman may be recognized as the surrogate decision-maker in some states.

Being familiar with the statute in one’s state is critical. Many surrogate statutes have restrictions on the circumstances under which they are applicable as well as on the types of decisions that surrogates are allowed to make (particularly regarding withholding or withdrawing life-sustaining treatments). In addition, most statutes require a court hearing if another family member challenges the decisions of the surrogate decision-maker recognized by the statute.

If there is no state surrogate statute, most jurisdictions require the appointment of a guardian. A guardian may also be required in states with statutes when the legally recognized decision-maker is being challenged by other family members. Another case in which appeal to the courts may be required is if no one knows the patient or agrees to serve as a surrogate. Other situations that usually require a guardian are the need to make any non-medical decisions (for instance, about financial matters) or when it is obvious that the duration of the patient’s incapacity will be prolonged. Deciding whether to petition for guardianship after a brain injury can be difficult and complex; the reader is referred to several useful reviews of the subject (27, 28).

To summarize, once it is determined that a person lacks decisional capacity, the first step is to identify a surrogate decision-maker. (Fig. 65-1) If the patient lacks the capacity to designate their own surrogate by executing



a DPAHC, one should ascertain whether or not an advance directive exists. If one doesn't (or if it is inapplicable), then the person identified by the relevant state statute is recognized as the decision-maker. If there is no surrogate statute (or if other family members disagree with the decision-maker recognized by a statute), then a guardian will need to be appointed. A guardian will also need to be appointed for all non-healthcare related decisions, since both advance directives as well as state surrogate statutes almost always apply only to healthcare decision-making.

While identifying a surrogate decision-maker is a necessary first step, the clinician also has an ongoing responsibility to ensure that the decisions made by the surrogate are appropriate. This means, first, that the clinician recognizes the limits to the types of decisions the surrogate can make (as specified in the laws of their jurisdiction). In addition, however, the clinician should also focus on the actual decisions made in order to ensure their appropriateness. In other words, the fact that the surrogate is legally empowered to make decisions on behalf of the patient does *not* mean that the surrogate is free to make any decision at all. There are ethical and legal guidelines that constrain the choices that a surrogate can make, and the clinician should be aware of whether these are being followed.

In general, there are two different principles that should guide the decisions made by a surrogate. These are known as the "substituted judgment" standard and the "best interests" standard. In exercising substituted judgment, surrogates are asked to make a decision as they think the patient would have made it. They are asked to put aside their own thoughts and feelings and choose as they believe the patient would have chosen based on their presumed knowledge of the patient's values, beliefs, desires, etc. Although a widely accepted standard, there are certain difficulties encountered in exercising substituted judgment.

First, there is a growing body of evidence documenting the difficulty that surrogates have in accurately predicting patients' wishes in particular situations (29–35). Even when the surrogates felt confident that they knew what their family members would want, these studies revealed a poor correlation between the surrogate's decisions and the patient's actual preferences. Although disturbing, these findings do not necessarily undermine the substituted judgment standard itself.

They do highlight, however, another important issue: what is the evidence for a patient's prior wishes? For instance, was the substituted judgment based on explicit and repeated statements by the patient or a single casual remark? Or does the substituted judgment simply represent an inference based on the patient's past behaviors or presumed values? In general, the most reliable evidence of a patient's wishes are prior statements by

the patient that are explicit and well considered. These statements are especially valid if it is known that the patient had direct or indirect knowledge of the condition in question (through the care of a family member, for instance). In addition, because evidence shows that preferences change over time, more recent statements are especially likely to be representative (36). For all these reasons, it becomes important to ask a surrogate how they came to their decision regarding what the patient would have wanted.

Even when one is confident about the patient's *previous* wishes, however, another, more fundamental problem may arise. Specifically, a person may change their mind after a brain injury. For instance, impairments that may have seemed intolerable to them prior to their injury may now come to be accepted (26). This shift may simply represent the fact that we did not really know what living with certain conditions was like. We all find it difficult, beforehand, to accurately imagine a condition significantly different from our own. In particular, there is a large body of evidence that documents how the able-bodied, including clinicians, significantly underestimate the quality of life possible after a disability, (26, 37–40) even when they live with someone with a severe disability (41).

Another reason that a person's preferences may seem to change after a brain injury is that their fundamental values, beliefs, and desires might, in fact, have been altered by the injury. This change in identity that some patients undergo was discussed earlier. In this context, it raises a fundamental issue: is it even appropriate to appeal to past wishes in making decisions for patients? We alluded to the controversy that surrounds this issue previously; the reader is again referred to several detailed examinations of this issue (25, 26, 34, 35).

Given some of the difficulties in exercising substituted judgment, another criterion is often utilized in evaluating a surrogate's decisions: the "best interest" standard. According to this standard, the criterion for making decisions is to do what is in the best interest of the patient. The primary role for the best interest standard is when the patient's previous wishes are not known. This is often the case in brain injury rehabilitation because few people anticipate having a brain injury, much less discuss with family members in advance what they would want done. In these cases, the decision that is made should be the one that is in the best interests of the patient, regardless of how the surrogate may actually feel about a particular decision.

Although intuitively appealing, the best interest standard faces its own set of difficulties. Specifically, what a person's best interests are and what would advance those interests is often a source of disagreement. One potential danger is that a family member, while well intentioned, may unconsciously project her own beliefs or values into the situation. This can be especially problematic when

seen in the light of the difficulty, discussed above, that we all have in imagining unfamiliar situations. In particular, the tendency of the able-bodied to underestimate the quality of life of the disabled can significantly distort the decisions of surrogates.

Another issue is the proper role of the family or caregivers' interests in decision-making. The rationale for both the substituted judgment and best interest standards is that they place the *patient's* interests first. Certainly, clinicians should be sensitive to any evidence that the family is making decisions based primarily on potential gain to themselves (e.g. financially). Yet, because the family or caregivers are greatly affected by the consequences of any decision made, it seems unreasonable to expect that their interests should have no role in decision-making.

As in many other difficult cases, the exact role that the families' interests play will vary from case to case and, even then, may be a source of reasonable and legitimate disagreement (34, 35). For instance, the placement of a patient in a nursing facility solely so that the family can have use of the patient's home is clearly wrong. On the other hand, it seems understandable when the same decision is made because the family member is a single, working parent unable to provide 24 hour care. It is important to acknowledge that these issues are not merely personal but also ones that have public policy and social implications. The lack of readily available social support systems, financial remuneration for caregivers, and viable community-based living alternatives for persons with brain injuries adds layers of complexity to any surrogate decision-making process.

In conclusion, after identifying the appropriate surrogate decision-maker, the clinician still has an ongoing responsibility to evaluate the decisions made to ensure that they represent what the patient herself would have wanted or, at least, are in the patient's best interests. If the clinician feels that the decisions made by a surrogate are not appropriate, every effort should be made to address and resolve this issue in discussions with the surrogate and other involved parties. Ethics committee consultations and/or consultation with legal counsel may also be needed to mediate conflicts and ensure adequate protection for vulnerable patients. If an ethics committee mechanism is used, it is desirable to ensure that persons who are knowledgeable about life with brain injury be included in the process. If these measures don't resolve the concerns, then appeal to the legal system may be necessary.

### BEYOND CONSENT: ASSENT AND DISSENT IN BRAIN INJURY REHABILITATION

While accurate, the process depicted in Figure 65-1 omits a crucial moral dimension of our approach to patients whose decision-making capacity is at question: the content

and quality of the conversations and interactions that precede the final decision. This is especially clear if we approach the process from the point of view of patients who decline or "dissent" from our recommendations. While it is true that we must ultimately honor the wishes of those patients who possess decision-making capacity, we are also morally obliged to engage them in conversation intended to understand their perspective and persuade them to re-consider their choice. Likewise, for patients who lack decisional capacity, it is still morally important that we attempt to secure their agreement or "assent" to the decisions that are made. In both cases, our commitment to our patients' welfare obliges us to make a significant effort, short of manipulation or coercion, to persuade them of the treatment plan. Although consent is the central concept in approaching decision-making capacity after brain injury, clinicians also need to be aware of the moral significance of assent and dissent (42).

By "assent", we refer to securing the agreement of a patient who does not have the decisional capacity to provide full informed consent. The concept of assent was first developed in the field of pediatrics, where it was recognized that children, although unable to give full consent, should still play some role in the decision making that surrounds their care. In fact, it has been urged that clinicians always attempt to secure the assent of children for treatment decisions, even though the parents have both the ethical and legal authority to make the actual decisions (43).

We believe that the concept of assent is also relevant to brain injury rehabilitation and that we should always make an attempt to secure the assent of decisionally incapacitated patients. This reflects a basic respect for and acknowledgement of the patient, despite the impairments in their decision-making. At a more practical level, a patient's assent is likely to increase patient compliance, especially with those treatments that require their active participation. Of course, there are situations in which assent is not relevant, such as in the minimally conscious patient. And there will be situations in which, in spite of the best efforts of the treatment team, patients may still refuse to give their assent to the treatment plan.

In these situations, it is generally acceptable to proceed with treatment, at least in the inpatient setting, especially if not proceeding leads to significant harm to the patient. Clearly, this only applies to those decisions where the patient is a passive recipient of treatment (for instance, receiving medications). If the treatment involves the active participation of the patient (such as engaging in physical therapy), forcing treatment is usually impossible and often morally repugnant. Addressing these issues in the outpatient setting is more complex and other legal considerations might apply (for instance, by virtue of the fact that the patient is no longer in a health care facility) and legal consultation may need to be obtained.

## SURROGATE DECISION-MAKING: THE SPECIAL CASE OF WITHDRAWAL OR WITHHOLDING LIFE-SUSTAINING TREATMENT FOR PERSONS WITH BRAIN INJURY

Surrogate decision making in the context of withdrawal of care raises issues that are not found for other health care decisions. Prior to the 1970's, disputes regarding the use of life-sustaining technologies were rare; indeed, in many cases these technologies were non-existent. With the growth and increased availability of technologies such as ventilators and gastrostomy tubes, questions about how and when to apply these technologies became commonplace (and, in fact, account for the impetus behind the growth in bioethics as a discipline). Patients with brain injuries were often front and center in such discussions. No case probably symbolizes the beginning of this era more than that of Karen Ann Quinlan.

Philosophers, theologians, ethicists, and health care professionals have disagreed over the years about whether there is a moral difference between withholding life-sustaining treatment (i.e. not initiating the life saving treatment) and withdrawing life-sustaining treatment, or taking away the treatment that is believed to be sustaining life (44). In general, there has been more recent consensus in the United States that they are morally equivalent acts (45, 46). In fact some would argue that to withhold the initiation of life-sustaining treatment because of a fear that a withdrawal decision may arise is dangerous, unwise, and not in the best interest of the patient. Sometimes (and brain injury is often one of these cases) only through the initiation of life-sustaining treatment can better prognostic information be clarified thus allowing a more considered decision about the on-going role of life-sustaining treatment if needed.

In the next section, we will briefly review some of the salient and often very public legal cases regarding persons with brain injuries in which questions of withdrawal of life-sustaining treatment arose. These cases have been chosen as we believe they help to illustrate some of the common law guidelines, cultural mores, and evolving moral discussions in this always complex, and often contentious, area of decision-making.

### Karen Ann Quinlan

In 1975, Karen Ann Quinlan, at the age of 21, sustained cardiac arrest and anoxic brain injury, resulting in permanent vegetative state (PVS). (We will use this phraseology to delineate a condition in which the patient lacks awareness of their environment and recovery is highly unlikely). In 1976, her father sought legal guardianship with specific authority to direct the withdrawal of her mechanical ventilation (47). The Supreme Court of

New Jersey granted him guardianship as requested and indicated that he could exercise on her behalf her right to privacy (i.e., to be free of unwanted medical treatment). In essence, if Mr. Quinlan and her family believed that Ms. Quinlan would not want to have her life supported by a ventilator, they could choose to have the ventilator withdrawn. The Court further stated that this decision was clearly based upon her *poor medical prognosis*—i.e. her state of PVS, believing that the “overwhelming majority of [society] would, we think, in similar circumstances, exercise such a choice in the same way for themselves or for those closest to them.”(47)

### Nancy Beth Cruzan

In 1983, Nancy Beth Cruzan was in a motor vehicle crash. She was also judged to be in a permanent vegetative state, and was fed via a gastrostomy tube. In 1986, her parents, acting as her guardians, initiated proceedings “to terminate her artificial nutrition and hydration.” Their request was based upon her poor medical prognosis for improvement as well as statements that she had made to a friend that “if sick or injured she would not wish to continue her life unless she could live at least halfway normally.” In essence, this case weighed 2 aspects of the due process clause of the 14th amendment to the Constitution: States are prohibited from “depriving any person of life, liberty, or property without due process of law.”(48) In other words, the first aspect was her *liberty right* to be free of unwanted medical treatment and the second was her *right to life*. The argument of the appellants (Nancy Cruzan's parents) was rejected by the Supreme Court of Missouri as not meeting the State's standard of “clear and convincing evidence”<sup>1</sup> of the incompetent person's wishes.

This case was reviewed by the U.S. Supreme Court in 1990 (49). The U.S. Supreme Court upheld a state's right to decide the standard of proof required before life-sustaining treatment can be withdrawn (most though not all have chosen the clear and convincing standard of proof). The Court also specifically commented on the role of surrogate decision-makers in the process, noting the difficulty that surrogates might have in executing decisions:

Close family members may have a strong feeling—a feeling not at all ignoble or unworthy, but not entirely disinterested, either—that they do not wish to witness the continuation of the life of a loved one which they regard as hopeless, meaningless, and even degrading. But

<sup>1</sup> Clear and convincing standard of proof has been defined as “proof sufficient to persuade the trier of fact that the patient held a firm and settled commitment to the termination of life supports under the circumstances like those presented” *In re Westchester County Medical Center on behalf of O'Connor*, 72 N.Y. 2d 517, 531, N.E. 2d 606, 613 (1988).

there is no automatic assurance that the view of close family members will necessarily be the same as the patient's would have been had she been confronted with the prospect of her situation while competent. Furthermore, "the State may also properly decline to make judgments about the "quality" of a particular individual's life and simply assert an unqualified interest in the preservation of human life to be weighed against the constitutionally protected interests of the individual" (49).

### Michael Martin

In 1987, Michael Martin sustained a head injury, leaving him with extensive cognitive and physical impairments. (50) He had a colostomy and a gastrostomy for nutrition and hydration. He was unable to take food orally. Mr. Martin lived in a nursing home, and communicated with head nods and gestures. In 1992, while being treated for a bowel obstruction, Mary Martin, his wife and guardian, contacted the hospital's bioethics committee to determine whether Mr. Martin's nutrition and hydration could be withdrawn. Based upon prior conversations, Mr. Martin was reported to say to his wife that he would rather die than be dependent on people or machines. In casual conversations on 2 occasions with co-workers he said he would not want to live if he were in a "vegetative state." The hospital ethic's committee issued a statement that withdrawal of treatment was both medically and ethically appropriate, but that it must be authorized by the court before the hospital would assist in withdrawal of treatment.

In contrast to Karen Ann Quinlan and Nancy Beth Cruzan, Michael Martin was *not* in a permanent vegetative state. Though he could understand short, simple questions, the medical experts all agreed that he lacked decisional capacity. Furthermore, Mr. Martin's sister contested Mary Martin's request and asked that she be removed as his guardian and conservator. Though Mary Martin was upheld as the guardian and conservator, the Michigan Supreme Court reversed the Court of Appeals decision in favor of withdrawal of medical treatment, concluding that there was not clear and convincing evidence that withdrawal of food and fluid is what Mr. Martin would want in his *current* condition: "To end the life a patient who still derives meaning and enjoyment from life or to condemn persons to lives from which they cry out for release is nothing short of barbaric. If we are to err, however, we must err in preserving life." (from 50 at 401–2).

Michael Martin's case is particularly interesting because he was neither terminally ill nor in a permanent vegetative state, which have been referred to as "condition-based thresholds" that some argue must be present before a non-treatment decision can be made. Though he had made some compelling statements about not wanting to live on machines or if in a vegetative state, he seemed content and did not indicate after his brain injury a desire to die. The Michigan Supreme Court ruled that to be clear

and convincing, the statements previously made needed to be a "serious, well thought out, consistent decision to refuse treatment under these exact circumstances, or circumstances highly similar to the current" (50).

### Robert Wendland

Robert Wendland, like Michael Martin had an extensive brain injury (in 1993 from a drunk driving accident) but was clearly not in a vegetative state. He was conscious but unable to talk. He was fed and given water through a gastrostomy tube and needed assistance with his activities of daily living. He lived in a nursing home in California. In 1995 his wife and conservator, Rose Wendland, petitioned the court for permission to withdraw his nutrition and hydration based upon statements that Mr. Wendland had made while competent that led her to believe he would not want to be sustained in his current state.

Like the prior cases, there was no written advance directive. The request was challenged by Mr. Wendland's mother and sister who brought suit to remove Rose Wendland as his conservator (51). Two critical issues emerged in this case: the threshold issue (and notably, for the first time, the language of "minimally conscious state" was being applied in court to describe the neurological state of the patient), and 2. the clear and convincing evidence standard was again challenged. Mr. Wendland died before the case could be decided by the California Supreme Court, but given the importance of the case they chose to issue a ruling clarifying and confirming that a "clear and convincing" evidence standard was necessary.

The case sparked a great deal of interest and a large number of amicus curiae briefs on both sides. Substantial support in favor of allowing Rose Wendland to withdraw Mr. Wendland's nutrition and hydration and thus lower the standard of evidence from clear and convincing to a preponderance of the evidence included the California Medical Association, the American Civil Liberties Union, and 41 bioethicists (52). Those opposed included a number of disability activists organizations including Not Dead Yet, ADAPT, the ARC, Brain Injury Association, Inc., the Disability Rights Center, The National Council on Independent Living, and the National Spinal Injury Association.<sup>2</sup>

<sup>2</sup> Not Dead Yet is a national grassroots organization of people with disabilities formed in 1996 to advocate against legalization of physician assisted suicide and euthanasia. ADAPT is composed of people with disabilities whose purpose is to advocate for the civil rights of people with disabilities to live in their homes and communities. The ARC is devoted to the welfare of persons with mental retardation and their families, and was instrumental in framing the ADA. The Disability Rights Center was established in 1978 to enable people with disabilities to live in society and secure their human and civil rights. The National Council on Independent Living is the oldest cross-disability grassroots organization run by and for people with disabilities.

### Terri Schiavo

In 1990, at the age of 26, Terri Schiavo sustained a cardiac arrest resulting in anoxic brain injury. In May of 1998, Michael Schiavo, Terri's husband and guardian, filed a petition in Florida to remove her gastrostomy tube. In support of the petition, Ms. Schiavo's husband presented testimony about statements Ms. Schiavo made before her arrest that he believed indicated she would not want to live in her current state (like the other cases reviewed, she did not have a written advance directive). Ms. Schiavo's parents, the Schindlers, who opposed the petition, objected to this testimony and also sought to have Mr. Schiavo removed as her guardian. In contrast to Nancy Beth Cruzan, Ms. Schiavo's neurological diagnosis of permanent vegetative state has been the subject of dispute, with medical experts on both sides disagreeing about her diagnosis and prognosis for improvement with further rehabilitation efforts (53). Specifically, the court placed the burden on the Schindlers to "establish that new treatment offers sufficient promise of increased cognitive function in Mrs. Schiavo's cerebral cortex—significantly improving the quality of Mrs. Schiavo's life—so that she herself would elect to undergo this treatment and would reverse the prior decision to withdraw life-prolonging procedures." The Second District Court of Appeals of Florida determined that there was not sufficient evidence presented to question her diagnosis of vegetative state or her poor prognosis for improvement (54). The appellate court also addressed the issue of family involvement in such decisions:

But in the end, this case is not about the aspirations that loving parents have for their children. It is about Teresa Schiavo's right to make her own decision, independent of her parents and independent of her husband. In circumstances such as these, when families cannot agree, the law has opened the doors of the circuit courts to permit trial judges to serve as surrogates or proxies to make decisions about life-prolonging procedures. It is the trial judge's duty not to make the decision that the judge would make for himself or herself or for a loved one. Instead, the trial judge must make a decision that the clear and convincing evidence show the ward would have made for herself (54).

After multiple appeals, legislative maneuvering, and much public dissension, Ms. Schiavo's nutrition and hydration was withdrawn and she died 13 days later on March 31, 2005 in a Florida hospice.

### SUMMARY

There are no simple guidelines for decision-making regarding the withdrawal and/or withholding of life sustaining treatment for persons with brain injury. The only

case of the five presented above that was reviewed by the U.S. Supreme Court, and thus has clear federal jurisdiction, is that of Nancy Beth Cruzan. The other cases were tried in the various states of New Jersey, Michigan, California and Florida, and are thus subject to the laws of each state. As each State is likely to have specific laws governing such decisions, it is imperative to be well-versed in state law and to consider consultation with legal counsel and ethics committees in the decision-making process. Many people will also find guidance from spiritual advisers or religious leaders to be very helpful and these resources should always be offered. Nonetheless, there are some generalizations and guidelines that we feel might be helpful in negotiating this difficult terrain:

1. It is important to know whether the person with a brain injury ever executed an advance directive. Are there written statements regarding the person's wishes for care and medical treatment? Did the person stipulate who they trusted to make decisions on his/her behalf if incompetent? Such directives have great moral and legal authority in this country, and in most instances are considered sufficient to satisfy evidence of "clear and convincing evidence" of a person's wishes. That is not to say, though, that an advance directive should be considered absolute and binding (26, 55). Specifically, while competency is required to make an advance directive, it is not necessarily a requirement for negating one. Thus, if a person with brain injury is able to reliably indicate that they no longer wish for their advance directive to be followed, then (in general) it should not be followed. (There are rare exceptions. For example, the Declaration for Mental Health Treatment in Illinois allows a person to sign an advance directive indicating they wish treatment including hospitalization, medication, electroconvulsive therapy, etc. if they have a mental condition requiring such treatment in the future, *even if they would refuse it at the time*) (56).
2. One of the critical questions in considering the withdrawal of life sustaining treatments involving persons with brain injury is: when is life with disability worse than death? These decisions inherently involve quality of life determinations by third parties, often invoking considerations of concepts of pain and suffering, the meaning of human life and personhood, concepts of "dignity," and economic considerations. While there is growing consensus among the legal, medical and bioethics communities that withdrawing life sustaining treatment is permissible when a person has permanent vegetative state in the US, there are still substantial minority voices that oppose this practice. There is also not a clear social consensus regarding whether withdrawal or withholding of treatment is

permissible in the absence of an advance directive when a person is not permanently unconscious; i.e., is minimally conscious or otherwise has severe brain injury.

3. It is imperative to establish a careful neurological diagnosis and provide the most accurate prognostic information possible. It is unlikely that a single, brief bedside neurological examination can establish with a high degree of certainty a diagnosis such as permanent vegetative state (PVS), and indeed, there is substantial evidence to show that an erroneous diagnosis of PVS is not an infrequent occurrence. (57, 58)
4. Given the complexities of brain injury, it is extremely important that health care providers with extensive experience with this condition (and in particular the rehabilitation phase) be involved in evaluating patients and providing information to families. For example, speech language therapists can help ferret out problems with communication that are due to sensory or motor impairments and not due to unconsciousness. Information about how people with brain injury (in general) adjust and experience their lives is also critical information, yet often missing from discussions of prognosis. While the experiences of a group cannot allow us to predict the experience of a single individual, it does provide a more complete, balanced and holistic view than a list of likely impairments.
5. Try to present information to families and surrogates in as balanced (i.e., neutral) a fashion as possible and avoid value-laden terminology. For example, the Glasgow Outcome Scale categories are highly value-laden, and thus potentially problematic. Only level five is considered a "good recovery," with moderate disability, severe disability, PVS, and death constituting the other four categories. These categories also are very broad and focus on the level of disability and not the level of handicap or life satisfaction, both of which are critically important to one's adjustment to brain injury (40).
6. Do not assume that all families feel equipped to provide care for their family member with a brain injury. In the U.S., it is not uncommon that families are expected to assume the responsibility for being caregivers—often at great personal expense, being asked to sacrifice jobs, other family responsibilities, and financial resources to meet the person's needs. It may be important to provide permission to the family member *not* to assume this role and to explore with families alternatives to support the person with brain injury in getting his/her needs met.

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# 66

## Life Care Planning After TBI: Clinical and Forensic Issues

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### INTRODUCTION

This chapter presents an overview of the tenets, methodologies, topics, and issues to be considered when evaluating the future medical, or life care, needs of the patient with acquired brain injury (ABI). Commonly known as a life care plan, the plan can be relatively short, with very little “medical” needs, or very complex and detailed, with multiple medical and rehabilitation needs outlined. For example, a patient may or may not have experienced a loss of consciousness, yet still exhibit clinical signs and symptoms suggesting long-term follow-up that affect vocational and social functioning but require little or no physician or medical needs (1,2). Although information relating to a wide range of brain injury conditions is included in this chapter, most details will be geared toward the patient who has multiple future care needs that justify an assessment for life care plan development.

A generally accepted and working definition for life care plan is:

*A life care plan* is a dynamic document based upon published standards of practice, comprehensive assessment, data analysis and research, which provides an organized concise plan for current and future needs with associated costs, for individuals who have experienced catastrophic injury or have chronic health care needs.

*Source:* Combined definition of the University of Florida and Intelicus annual life care planning conference and the American Academy of Nurse Life Care Planners (now known as the International Academy of Life Care Planners) presented at the Forensic Section meeting, National Association of Rehabilitation Professionals in the Private Sector (NARPPS) annual conference, Colorado Springs, CO, and agreed upon April 3, 1998 (3).

As a “dynamic document,” medication changes and other updates can be expected over time. As will be seen below, however, life care plans, when completed according to established procedures, are a reliable document.

### HISTORY

Life care planning first appeared in the legal publication, *Damages in Tort Action* (4), which established the guidelines for determining damages in civil litigation cases. By 1985, the life care plan was introduced to the health care industry in *A Guide to Rehabilitation* (5). One of the first rehabilitation professional training programs was organized by Dr. Paul Deutsch and offered on September 16–17, 1986, in Hilton Head, SC, where more than 100 rehabilitation professionals from throughout the United States, including one of this chapter’s authors, assembled



to begin the process of setting standards for development of life care plans.

In the fall of 1992, five rehabilitation professionals—Richard Bonfiglio, MD; Paul Deutsch, Ph.D.; Julie Kitchen, CDMS; Susan Riddick, RN; and Roger Weed, Ph.D.—met to discuss issues associated with the life care planning industry. Concerned that fragmentation and poor standardization would result in an overall decline of the industry, the group developed a concentrated training program representing the various aspects of life care planning (3).

After designing the program, a management company (Rehabilitation Training Institute) was contracted to set up training programs throughout the United States. Before the announcements were fully distributed, the first of the organized tracks was filled. It appeared obvious that there was a number of rehabilitation professionals interested in pursuing advanced education related to life care planning, and several participants requested official recognition for their educational efforts. Dr. Horace Sawyer of the University of Florida agreed to pursue an official certificate of completion through the University of Florida's Continuing Education Department. As a result, a private/public partnership between the Rehabilitation Training Institute and the University of Florida was formed and named Intelicus. The five founders donated the program content to Intelicus. Some even continue today as faculty, although they no longer have control over program content or management. Over the years, these courses have been adjusted to focus on the roles and responsibilities that more specifically identify with life care planners based on research and participant comments. Most recently, the Intelicus life care planning training program was purchased by MediPro Seminars, LLC, to continue to offer life care planning advanced training, as well as the annual international life care planning conference. (See [www.mediproseminars.com](http://www.mediproseminars.com).)

Although the certificate from the University of Florida added value to obtaining education specific to this specialty practice, it did not provide the assurance of ethical practice or the professional identity desired by people who had invested thousands of dollars and many hours of their time in the training process. Ultimately, the Commission on Disability Examiner Certification (now known as the Commission on Health Care Certification, or CHCC) based in Midlothian, Virginia, and directed by V. Robert May, Rh.D., assumed the responsibility in leading the way to certification. Because of his efforts, the first national certification in life care planning (i.e., Certified Life Care Planner) was offered in 1996. Currently, several organizations have approval of the certification Board to provide training leading to certification and/or continuing education training for certification maintenance. Also, in the 1990s, the International Academy of

Life Care Planners was formed (previously known as the American Academy of Nurse Life Care Planners), and in 2002, the *Journal of Life Care Planning* and the Foundation for Life Care Planning Research were launched. Life Care Planning Summits also have been held bi-annually since 2000 to discuss and reach consensus on many topics of importance to ethical life care planning practice.

Over the years, life care plans have been expanding into a variety of fields including but not limited to managed care, workers' compensation, civil litigation, mediation, reserve setting for insurance companies, estate trust fund planning, gerontology care, and federal vaccine injury fund cases, all of which include individuals with brain injury in the patient population (6–11).

The range of future care needs can differ significantly depending on a mild, moderate, or severe brain injury. Individuals with mild brain injury, for instance, may not require a comprehensive life care plan and may be less likely to need all of the care commonly considered for a life care plan. Nevertheless, there may be value in utilizing the standardized approach in these cases to assure a comprehensive evaluation is done. For details with regard to definitions and functional deficits for individuals with mild acquired brain injury, the reader is referred to Goldberg's chapter on Post-Concussive Disorders found elsewhere in this book.

Patients with mild or moderate brain injury can have few, if any, physical problems. Therefore, the physician or medical team may not be an integral part of the future care planning. Instead, the case manager, neuropsychologist, vocational expert and, perhaps, the family or other support system, will be the most relevant participants in the life care planning process. However, it is not uncommon for an individual with mild to moderate head injury to also have musculoskeletal problems including fractures, facial damage (which may or may not be repairable), seizures, and other physiological deficits (12). On the other hand, patients with more severe brain injury often have multiple and obvious physical impairments as well as more severe cognitive deficits and require multiple physicians, life-long medical care, and multiple supply, medication and equipment needs. Obviously, an effective life care plan will include items for all treatable deficits that are related to or a result of the ABI.

In order to assure that the rehabilitation consultant addresses all appropriate issues for earning capacity analysis, it is helpful to utilize a standard methodology such as RAPEL (2, 3, 8, 9, 13). RAPEL is a mnemonic to help ensure the relevant "damages" of a case are evaluated. Adapted for pediatric cases, PEEDS-RAPEL<sup>®</sup> expands the RAPEL method and analyzes relevant data specific to the child with a disability, i.e., P (parental/family occupations), E (educational attainment), E (evaluation results), D (developmental stage), and S (synthesis). For further discussion

on PEEDS-RAPEL<sup>®</sup> for pediatric case evaluation, the reader is referred to Neulicht & Berens (14).

Although all sections of RAPEL will be discussed in this chapter, only one part, the Rehabilitation plan, is directly related to the life care plan.

### RAPEL APPROACH

When developing a reasonable opinion for forensic cases, it is expected that the rehabilitation consultant follow a standardized assessment approach to provide the appropriate information for the patient, patient's family, attorney, and economist. Certain specific requirements are necessary in order to satisfy all of these issue and although methods for determining the cost for future care as well as vocational and hedonic damages have been published

(6, 15, 16), it appeared that a comprehensive "common sense" approach encompassing both needs was lacking. The RAPEL method, representing five primary issues relating to future care needs and earnings capacity analysis (see Table 66-1), was designed to address rehabilitation needs and provide a "road map" of care, as well as generate a "bottom line" figure based on future care needs and earnings capacity analysis for persons with a catastrophic injury, including ABI.

The first of the RAPEL topics is as follows:

**R = Rehabilitation Plan.** The patient's vocational and functional limitations, strengths, emotional functioning, and cognitive capabilities are assessed utilizing information gathered from treating professionals or other experts listed in this chapter. This may include additional future testing, counseling, training fees, rehabilitation technology, job analysis, job coaching, placement, and

**TABLE 66-1**

*The RAPEL Method: A Common Sense Approach To Future Care and Earnings Capacity Analysis*

<b>Rehabilitation plan</b>	Determine the rehabilitation plan based on the patient's vocational and functional limitations, vocational strengths, emotional functioning, and cognitive capabilities. This may include testing, counseling, training fees, rehab technology, job analysis, job coaching, placement, and other needs for increasing employment potential. Also consider reasonable accommodation. A life care plan is appropriate for catastrophic injuries.
<b>Access to the labor market</b>	Determine the patient's access to the labor market. Methods include skilltrait ( <a href="http://www.skilltrait.com">www.skilltrait.com</a> ) or various other computer programs, transferability of skills (or worker trait) analysis, disability statistics, and experience. This may also represent the patient's loss of choice and is particularly relevant if earnings potential is based on very few positions.
<b>Placeability</b>	This represents the likelihood that the patient could be successfully placed in a job. This is where the "rubber meets the road". Consider the employment statistics for people with disabilities, employment data for the specific medical condition (if available), economic situation of the community (may include a labor market survey), availability (not just existence) of jobs in chosen occupations. Note that the patient's attitude, personality, and other factors will influence the ultimate outcome.
<b>Earnings capacity</b>	Based on the above, what is the pre-incident capacity to earn compared to the post-incident capacity to earn. Methods include analysis of the specific job titles or class of jobs that a person could have engaged in pre- vs. post-incident, the ability to be educated (sometimes useful for people with acquired brain injury), family history for pediatric injuries, and computer analysis based on the individual's worker traits. Special consideration applies to children, women with limited or no work history, people who choose to work below their capacity (e.g., highly educated who are farmers), and military trained.
<b>Labor force participation</b>	This represents the patient's work life expectancy. Determine the amount of time that is lost, if any, from the labor force as a result of the disability. Issues include longer time to find employment, part-time vs. full-time employment, medical treatment or follow up, earlier retirement, etc. Display data using specific dates or percentages. For example, an average of four hours a day may represent a 50% loss.

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other needs for improving the patient's potential for employment. Future medical care is also addressed here and typically is displayed in a life care plan for individuals with a catastrophic injury.

One commonly observed problem for forensic cases is the lack of specific data to conscientiously determine a complete lifetime cost. Many professionals who write reports expect that a re-evaluation will take place in one to two years, at which time additional recommendations will be made. However, in personal injury litigation, it is important to determine, as much as possible at the time of plan development, all of the issues that are expected to be addressed throughout the patient's lifetime. Generally, it is recommended that the rehabilitation consultant meet or communicate with the patient's treatment team (if able) or other appropriate experts associated with the case to discuss the case in detail, rather than rely upon written reports or other records. Extensive rehabilitation plans may best be addressed through a detailed assessment of lifetime needs; i.e., the life care plan. The life care plan is a published format designed to outline appropriate future care details (3, 4, 6, 9, 10).

### ELEMENTS OF THE LIFE CARE PLAN

First, it is important to understand that a variety of formats have been developed to display patient needs. In the original texts and books, the topics listed below were suggested and are still used today. The important aspect is to assure that all topics below are considered, as appropriate, in effective life care planning.

1. *Projected Evaluations.* Intended to describe non-physician evaluations that will occur on a periodic basis. These may include evaluations in physical therapy, speech therapy, recreational therapy, occupational therapy, music therapy, dietary assessment, audiology, vision screening, swallow studies, and others. The information displays specific recommendations, frequency over lifetime, and expected costs.
2. *Projected Therapeutic Modalities.* After projected evaluations have been completed, recommendations for ongoing treatment will be offered. With patients who have a catastrophic brain injury, it is common to include physical therapy, speech therapy, occupational therapy, family education, counseling, etc. This page identifies which non-physician treatment is recommended, over a specific period of time, at what frequency, and what cost.
3. *Diagnostic Testing/Educational Assessment.* Generally speaking, people with a catastrophic brain injury will undergo a variety of diagnostic testing, including neuropsychological, psychological, vocational evaluation, and, in the case of children, psycho-educational testing. Often evaluations will occur at specific points in a patient's life which would be identified by listing the years at which the evaluation would take place. For example, a child might be tested psychologically at ages that coincide with certain developmental stages or specific educational milestones. Such milestones may be the beginning of school, onset of puberty, beginning of high school, and entering employment or transitioning to adulthood. Consideration also should be given to additional evaluations that may be indicated as the patient ages, such as between age 50–60.
4. *Wheelchair Needs.* This page includes the type and configuration of wheelchairs the patient requires. For example, people who are tetraplegic often require a power wheelchair that reclines or tilts in space. The individual accesses and controls the wheelchair in a variety of ways, including joystick, sip and puff, head tilting, voice control, and others. The specifications will allow the life care planner to research costs from a variety of vendors (18). Some patients with hemiparesis may prefer a scooter for mobility assistance and some with less severe brain injuries may be ambulatory for short distances but need a light-weight manual wheelchair for longer distances.
5. *Wheelchair Accessories and Maintenance.* Each wheelchair requires certain accessories such as cushions for skin care, lap tables, carry bags, and other potential custom features. In addition, the wheelchair, depending on amount of use, requires maintenance. Maintenance can be very expensive for power wheelchairs, like the iBOT™, or inexpensive for wheelchairs which are used only for back-up purposes and are lightly used.
6. *Aids for Independent Function.* Many individuals with a brain injury have restricted ability to use their bodies and can make use of certain items for independence. A common example is the environmental control unit (ECU) or system that allows the patient to turn lights on and off, open and close doors, start and stop computers, turn on/off televisions, radios, fans, etc. Some less expensive adaptive aides may include reachers which will allow an individual to grasp items on a shelf or on the floor without having to stand up or bend over.
7. *Orthotics and Prosthetics.* With regard to significant brain injury, many patients will require braces or ankle/foot orthosis (AFO) to help with contractures, decrease spasticity, etc. Sometimes these braces, when custom designed, are costly and, over an individual's lifetime, can add up to a significant amount of money. Prosthetics generally are needed for individuals with one or more amputations. Prostheses

also require accessories (e.g., socks, liners, cosmetic covers, etc.) and will need replacement and ongoing maintenance over the patient's lifetime. The cost for all of these items, as well as applicable maintenance and replacement schedules, will be included on this page.

8. *Home Furnishing and Accessories.* Often a patient living at home will have need for a specialty bed and skin care mattress or powered lift and recline, portable ramps for accessibility, patient lift systems, etc. This section will require a specific inventory of the patient's needs at home or in their place of residence.
9. *Drug and Supply Needs.* This page includes prescription and non-prescription medication and supplies as related to or a result of the brain injury. As an example, a patient who is in a persistent vegetative state will likely need catheters or adult diapers, skin care products, and medications for various injury related problems or complications.
10. *Home Care/Facility Care.* Philosophically, it is more desirable to have a patient live in the least restrictive setting possible. This alternative also is a way to reduce complications from diseases from other patients that are common in a facility setting, as well as to improve the emotional status of the patient. However, this may not be the most cost effective alternative nor, in some cases, the most medically appropriate. Facility care, generally, is not as responsive to an individual as a custom-designed home care program; however, some individuals have no capability of living at home, or their needs exceed those which are available in a home environment. In this situation, facilities for individuals with serious behavioral disorder or those in persistent vegetative state as a result of acquired brain injury may be the most appropriate. There also may be need for specialty programs such as yearly summer camps, especially for children and adolescents. The level of in-home care also should be identified. For example, some individuals need only occasional home care or a time specific amount each day (i.e., 4 hours per day) while other patients need 24-hour, high-tech, nursing care.
11. *Future Medical Care: Routine.* Probably the most common routine medical care for individuals with acquired brain injury is provided by a physiatrist. The frequency of visits will depend on the medications, complications and severity of the injury. A person on antiseizure medication may be seen several times per year to evaluate the blood level and efficacy of the drug. Routine medical care also may include annual evaluations by the various specialty(ies) that may be appropriate for the severity of the brain injury. For instance, in dual diagnosis cases where the individual has both a brain injury and a spinal cord injury, the patient may need a routine annual evaluation by psychiatry, urology, dermatology, orthopedics, neurology, and others, as well as X-rays and lab work or diagnostic tests (e.g., urodynamics). This page summarizes those needs.
12. *Transportation.* Transportation needs vary substantially from patient to patient. Some individuals need little or no modification to their vehicles and may only require mileage reimbursement for injury-related appointments. Others may have a need for adding hand controls to their present vehicle. Yet other individuals may need a custom-designed van with lift and wheelchair tie-downs and rely on a driver for all driving activities or be able to drive with highly sophisticated technology such as the Digi Drive system (19).
13. *Health and Strength Maintenance.* This page, titled Recreation and Leisure Time Activities in the original literature, is designed to identify specialty recreation needs, adaptive games, and devices that will allow patients to be as active as possible and engage in health improving therapeutic action. Activity is very important to the physical and emotional well-being of a patient and such activities are often adjunctive to, and less expensive than, hiring a physical or occupational therapist. Specialty sports-related wheelchairs (such as basketball, tennis, and other custom-designed chairs) should not go on this page, but instead should be placed on the Wheelchair page. For more information on Health and Strength Maintenance, see *Support for Recreation and Leisure Time Activities in Life Care Plans* (20).
14. *Architectural Renovations.* If the patient is to be cared for at home, significant and comprehensive architectural renovations often will be required depending on the extent of the injury and the patient's functional limitations. For example, a patient who uses a wheelchair for mobility will need ramps (preferably at two entries into the home), hallways may need to be widened, the kitchen may require modification, fire or smoke detection will be needed, specialized floor coverings may be installed, bathrooms may be enlarged, equipment and attendant rooms may be added, and an emergency exit out of or near the bedroom may be added. Hablutzel and McMahon (21) published architectural renovation standards based on the Americans with Disability Act for those who wish to read more about this area.
15. *Potential Complications.* Costs of Potential Complications are not included in the total cost of the life care plan, presumably because effective life care planning will reduce potential complications as it provides the structure for quality care. On the other hand, it is important for people to understand what common

complications are involved with a particular disability (i.e., acquired brain injury). In the case of people with significant ABI, they are at higher risk to re-injure themselves due to poor balance or judgment and lack of safety awareness. Also, individuals with severe brain injury or who are in a persistent vegetative state often have skin breakdown, cardiovascular difficulty, pulmonary diseases, etc. Individuals on long-term Dilantin anti-seizure medication often have gum disease or other dental problems. Poor psychological adjustment to the person's disability often is the direct result of poor environment, poor care, or inability to engage in meaningful activities (22).

16. *Future Medical Care/Surgical Intervention or Aggressive Treatment.* In some situations the patient will have known needs for aggressive care. Commonly known problems for people with a brain injury include plastic surgery, dental restoration, time-limited rehabilitation programs, and short-term inpatient brain injury "tune-ups" (episodic one to four week rehabilitation programs). To be placed on this page, it is expected that these services are more probable than not to occur and occasional or time-limited treatment.
17. *Orthopedic Equipment Needs.* Some patients will need specific orthopedic equipment, such as body support equipment, walkers, or standing table. This is frequently termed "durable medical equipment."
18. *Vocational/Educational Plan.* This page was not included in the original life care planning literature and was later added to specifically address future vocational and educational or training needs. The professional involved in developing the life care plan may not be responsible for addressing this portion of the patient's future care if he/she is not qualified to assess these issues. Additionally, other qualified professionals may choose to complete a narrative report and a specific rehabilitation plan that focuses on vocational issues in a separate document. It is the authors' opinion that this page should be included in the life care plan in the same way that allied health recommendations are included, since overlap or "falling between the cracks" can otherwise result. This page obviously should include recommendations for vocationally-related items such as job coaching, supported employment, vocational counseling, tuition/fees, books and supplies for training programs, rehabilitation technology, and/or specialized educational programs, as well as the cost of each item.

### The Life Care Planning Team

In many ways, developing a comprehensive life care plan is much like completing a puzzle and making sure all the

pieces fit together to complete the picture (11). The following individuals and professionals commonly have a role to play in the life care planning process and may or may not be involved in any given case. (Note: in forensic cases when developing a defense plan, the treating team, patient and others may not be available to the life care planner.)

- **Patient** (i.e., the person with the disability). Assuming that the patient is accessible (i.e., legally permitted) and capable of appropriate interaction, interview and listen to him or her. Legally permitted in this context refers to the potential that defense experts in some states do not always have the "right" to interview patients and, therefore, do not have access to meet or talk with them. In cases where the patient is interviewed, it is the authors' experience that during the interview, patients often will demonstrate deficits or discuss their problems in reasonable detail. For cases where an interview does not occur, one possible alternative is to have the attorney ask standard interview questions via deposition. A videotaped "Day in the Life" of the patient also is helpful to review. An important point to make is that defense "consultants" are not disclosed and, therefore, will not interview patients. It is also recommended that the patient interview take place in the person's residence (home or facility). In the authors' opinion, patients are less inconvenienced and more comfortable in their normal setting. Secondly, for patients with numerous supplies, medications and equipment requirements, this procedure maximizes the potential for a comprehensive assessment of needs, including a review of potential architectural needs.
- **Family members/caregivers.** Similar to the patient interview, life care planners commonly interview and listen to the family (if legally permitted) involved in the patient's care. It is not uncommon for patients with a brain injury to be unable to describe in adequate detail the difficulties that they experience, and the family can help to "paint the picture." In addition, family support often is very important to ultimate outcome.
- **Medical evaluation.** Medical evaluation(s) with appropriate medical specialists should include an assessment of the patient's functional limitations, expected future medical treatment including referral to other specialties, a review of medications, supplies, and/or durable medical equipment, as well as related topics (see Table 66-2 for suggested questions).
- **Physiatrist.** Many patients with mild to moderate brain injury will have few, if any, long term *medical* needs. However, for major injuries, a physiatrist who specializes in long term brain injury rehabilitation can be designated the team leader for many of the

**TABLE 66-2**  
**Example Questions for Physicians: Life Care Plan Only**

1. Future Care (Distinguish what is reasonable and appropriate vs. medically necessary vs. desirable.)
  - How long will the patient need follow-up?
  - When will the patient reach maximum medical improvement?
  - How long and how often will treatment be needed? (Include frequency and duration, e.g., every six months for 2 years then once per year thereafter, etc.)
  - What treatment is expected? (Follow-up visits, routine evaluations, etc.)
  - How much will each visit cost?
  - Are X-rays or lab work needed? If so, how often and how much will each cost?
  - Do you anticipate any further surgeries or aggressive medical treatment; e.g., several years from now due to complications? If so, what, when, and how much will each cost?
2. Possible Complications  
What complications are possible/expected? (Traumatic arthritis, contractures, adverse reactions to medications, seizures, spasticity, earlier onset of aging-related dementia, maladaptive behaviors, additional injury due to reduced physical skills or poor judgement, etc.)
3. Recommended Medical Follow-up By Other Specialties
  - Orthopedist?
  - Neurology?
  - Physiatrist?
  - Cosmetic Surgeon?
  - Dermatology?
  - Psychology/Neuropsychology?
  - Occupational Therapist, Physical Therapist, Speech Therapy, Dietary, Recreation Therapy?
  - Other?

If you recommend any of the above, do you have an opinion regarding what treatment will be needed, how often it will be needed, and expected costs?

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specialties listed below, and a team may be assembled which includes physicians who address specific areas, such as plastic surgery, pulmonology, orthopedics, etc. As cited in Weed (3), in general, the physiatrist will be the best physician to establish a medical foundation for a life care plan (23, 24). As noted by Zasler (24), "All too often physicians may not be fully versed in life care planning. It is therefore critical that life care planners communicate in an appropriate and timely manner to assure that their role in a particular case is understood" (p. 57). One way to assure that future care information is properly solicited is to utilize the example questions checklist in this chapter. For physicians, if recommending a life care plan for a patient, or if meeting with an already assigned life care planner for one of his/her patients, it is recommended that the person conducting the life care planning assessment be asked if he/she is board certified as a life care planner (specifically if they are a CLCP). The goal of this questioning is to increase the likelihood that the life care plan is developed according to existing standards.

- **Neuropsychologist.** The neuropsychologist can play an invaluable role in evaluating the long-term effects of the brain injury on the patient's ability to

function (25). It is within the role of the life care planner to refer a patient for a neuropsychological evaluation in cases where there is documented or suspected brain injury/impairment (26). A specialized list of questions to help the life care planner prepare a life care plan, including address future vocational/educational issues, has been developed to assure that the appropriate questions are asked during the evaluation (see Table 66-3). Asking the right questions is important because many neuropsychological evaluations do not seem to be geared toward identifying long-term future care needs or rehabilitation strategies to maximize the patient's ability to function in society or participate in gainful work.

- **Occupational therapist.** The occupational therapist may be an appropriate referral for an assessment for seating and positioning, adaptive aids, safety in the residence, and other vocationally-related issues (27). For some patients, activities of daily living training, including household safety, would be included.
- **Speech and language pathologist** (may also be called Communication Disorders Specialist). The qualified speech and language pathologist is instrumental in assessing augmentative communications for patients with more severe communications disorder, as well

**TABLE 66-3**  
**Neuropsychologist Questions**  
(with credit to Robert Fraser, Ph.D.)

In addition to the standard evaluation report, add the following as appropriate.

1. Please describe, in lay terms, the damage to the brain.
2. Please describe the effects of the accident on the patient's ability to function.
3. Please provide an opinion to the following topics:
  - a. Intelligence level? (include pre- vs. post-incident if able)
  - b. Personality style with regard to the workplace and home?
  - c. Stamina level?
  - d. Functional limitations and assets?
  - e. Ability for education/training?
  - f. Vocational implications - style of learning?
  - g. Level of insight into present functioning?
  - h. Ability to compensate for deficits?
  - i. Ability to initiate action?
  - j. Memory impairments (short-term, long-term, auditory, visual, etc.)?
  - k. Ability to identify and correct errors?
  - l. Recommendations for compensation strategies?
  - m. Need for companion or attendant care?
4. What is the proposed treatment plan?
  - a. Counseling? (individual and family)
  - b. Cognitive therapy?
  - c. Re-evaluations?
  - d. Referral to others? (e.g., physicians)
  - e. Other?
5. How much and how long? (Include the cost per session or hour and re-evaluations.)

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as assessing receptive/expressive speech and language abilities, and identifying cognitive remediation professionals (28).

- **Physical therapist.** A physical therapist is often the most appropriate referral to determine the patient's true physical capabilities by compiling a functional capacity assessment that is more detailed than most physicians can report (29). For example, Ergos™ equipment has become quite sophisticated, as has Lido™, Cybex™, and other equipment designed to identify the individual's physical and functional capabilities.
- **Educational consultant.** For the school-aged patient, an educational consultant can be very important to maximize the patient's educational potential. Under the federal Individuals with Disabilities Education Act (IDEA), the public school system is responsible for providing specialized services to eligible school-age children with disabilities through age 21, if appropriate. Additionally, each state offers early intervention programs for children from birth to age 3. However, many of these school-aged children are poorly served for a variety of reasons. One may be that the child has not been adequately assessed in order to identify deficits that would meet the criteria for specialized education. Another is that the

child may meet the eligibility requirements but the school's funding is inadequate and the school fails to provide appropriate support. Another potential for dispute may be the school's contention that therapy is required for "medical" purposes rather than "educational" and the school, therefore, will not provide the services. Educational consultants who are familiar with the rules often can negotiate the appropriate education protocol which would then be included in the life care plan.

- **Vocational evaluator** (if there is work potential). A vocational evaluator can establish standardized protocols for assessing the patient's vocational capabilities, including aptitudes, interests, temperaments, and other related information (25). For the patient with a brain injury, a "real work" situational assessment or on-the-job evaluation may be more appropriate than formal timed or time-limited testing. The evaluator should have at least a Master's degree and experience working with individuals with a brain injury. A Certified Vocational Evaluator (CVE) is the recommended specialty for this assessment.
- **Rehabilitation counselor.** A rehabilitation counselor with a Master's degree or higher from an accredited rehabilitation counselor training program should be involved to assist in arranging for

a job analysis, labor market surveys, vocational guidance and counseling, selective job placement, and/or supported employment, and is often the true coordinator of services (25, 30). Indeed, for purposes of this chapter, the rehabilitation consultant for the patient with a mild to moderate brain injury is likely the prime candidate to take the information generated by the specialties listed above and develop it into a rehabilitation plan and earnings capacity analysis. A Certified Rehabilitation Counselor (CRC) is recommended, although a CVE (see above) may also have the expertise to provide this service.

- **Economist.** In most situations, the life care planner or expert witness, in forensic cases, will work with an economist. The economist will rely upon the base costs in the life care plan to project the cost of care throughout the patient's life expectancy (16). This specialized industry is sophisticated and complex. The rehabilitation professional who does not have an education in economic forecasting is sometimes requested to project life care plan costs in personal injury litigation cases, and it is the authors' opinion that this is a dangerous practice in most instances. It is important to know, for example, what the different rates of inflation are for medical and non-medical care, as well as discounts to present value methodologies. In most cases, the economist will be necessary as they are well-versed and educated in inflation rules and investment strategies. On the other hand, there are a few states that endorse the "Alaska Rule" which assumes that inflation and reasonable investment rates are essentially equal and "wash out" each other such that an economist may not be needed in those cases. In summary, it is strongly recommended that the life care planner defer to an economist or other trained and qualified professional for the ultimate cost of the life care plan, unless he or she has specific training in this specialized area.

As a general rule, in order for an economist to project the cost of care, certain details must be included. In the authors' experience, many health care providers offer opinions that a patient will require follow-up services for "a long time;" however, it is not possible to identify specific costs for patient needs when the time frame is not quantified. In order to obtain a "bottom line" cost for the care plan, the professional must obtain the following information:

- expected type and amount of treatment (frequency)
- date to start treatment
- date to stop treatment
- base cost of treatment (in today's dollars)

See Table 66-4 for an example entry that contains the minimum required data to calculate future costs.

**TABLE 66-4**  
*Example Minimum Information Needed for Economist to Project Costs*

Psychological Evaluation 6/2005 at a cost of \$600.  
Expect counseling to start 7/2005, one time per week, one hour session each for 26 weeks at a cost of \$100 per hour.

Expect group counseling one time per week for 2 years, beginning 1/2006 at a cost of \$40 per session.

Expect medical follow-up four times per year by psychiatrist at a cost of \$150 for the initial visit, then \$75 each visit until 1/2007.

Medication prescribed is Prozac, one 20 mg. per day, from 7/2005-1/2007, at a cost of \$53.86 for 30 pills.

Occasionally, identifying the frequency and duration of activities can be very complex. Pediatric brain injury cases often will include needs for periodic speech, occupational, and physical therapy which may begin and end at specific developmental periods in the child's life (27-29). Although these therapies may be provided through the school system while the child is in school, private or medically based therapies often are indicated to address the child's needs outside the education setting for the following reasons: (1) to augment school-based services, (2) to address the child's needs at home and in the community, (3) to prevent or reduce medical complications, and 4) to provide continuation of therapies throughout the summer to assure maintenance and carry over of skills into the next developmental stage. By knowing what services are provided by the school system, the life care planner can better determine what additional services the child needs outside the school environment to achieve short and long-term goals (31). For instance, occupational therapy may be needed for activities of daily living for a six-year-old child and then be discontinued throughout school years until the child is ready to enter the work world at which time an occupational therapist may rejoin the treatment team in order to furnish assistive devices for work-related activity. A challenge for life care planning is that sometimes treatment team professionals fail to consider the life-time needs of a patient, since they are most often involved in care lasting only one to two years.

To continue with an explanation of the RAPEL method previously described:

**A = Access to Labor Market.** In many cases involving individuals with ABI, the patient may very well be able to return to a job that is custom-designed around his/her disability or with an employer who is interested in hiring an employee with mild to moderate cognitive deficits. However, the patient may not have access to the



same number or level of vocational choices as he or she did prior to the injury. In essence, it may be that the patient would appear to have no particular loss of earnings capacity, but at the same time be at high risk for losing a job and then having a significant problem locating alternate suitable employment. Access to labor market can be determined through the services of a qualified rehabilitation consultant and is beyond the scope of this chapter.

**P = Placeability.** Placeability represents the likelihood that the patient will be successfully placed in a job with or without rehabilitation or rehabilitation consultant assistance. One may need to conduct a labor market survey, job analysis, or, in pediatric cases, rely upon statistical data to opine about ultimate placeability as an adult. In some situations, the economic condition of the community also may be a factor. It is important that the rehabilitation consultant recognize that the patient's personality, cognitive limitations, and other factors certainly influence the ultimate outcome. For adults, the rehabilitation consultant generally should include an opinion about jobs that are available (actual openings) in addition to jobs that exist but are not currently available to the patient.

**E = Earnings Capacity.** Based on the rehabilitation or life care plan, access to the labor market, and placeability factors, the patient may or may not be employable in the labor market. If employment is likely, an estimate of the earnings potential is included as a mitigating factor in determining damages. In addition, identifying the pre-incident earnings capacity is a necessary element of determining what is included in the life care plan since jurisdiction "rules" will determine certain needs. For example, if the life care plan is being prepared for a patient related to a vaccine injury fund case, then general living costs (housing, food, transportation, etc.) will be part of the plan, whereas these costs generally are not included in personal injury cases.

**L = Labor Force Participation.** This category represents an opinion about the patient's expected work life expectancy or amount of time expected to be in the work force. Usually an individual who has a reduced life expectancy also will be expected to have a reduced work life expectancy. At the other end of the spectrum, the patient's participation in the labor force may be unchanged after the brain injury. Or, an individual may have the capacity to work six hours per day rather than eight hours per day, which represents a 25% loss of normal work life expectancy. Other patients may require a longer period of time to find a job or have longer time off between jobs as a result of the ABI and this could have an impact on their worklife expectancy. Further, some patients, pre-injury, may have demonstrated consistent extra income by working overtime hours or at a second job and this situation should be considered in the analysis as well.

In summary, the RAPEL method identifies the minimum data needed for determining damages in personal injury litigation and provides the data needed for economists to arrive at a bottom line figure.

## GENERAL LIFE CARE PLANNING PROCEDURES

As a first step, the life care planner must request and receive all medical records and consultations (9, 18, 32, 33). If the individual is involved in litigation, depositions of health care professionals often are available and useful to review as related to damages and/or future care needs. If information is unclear, confirmation of diagnosis is essential. As previously noted, if the patient resides at home, it is recommended that the interview take place in the residence rather than in an office or other location so that a complete inspection of the individual's needs can be done. It is unlikely that the patient and/or family member(s) will remember all of the drugs and supplies, and an on-site inventory is the most effective way to determine the patient's current needs. In addition to an inventory of medications, supplies, and equipment during the initial interview, information is obtained with respect to the patient's pre-incident medical and social history, family history, current physical and emotional status (including limitations), medical treatment, socioeconomic status, employment history, and long-term plans. A thorough assessment usually requires several hours to complete.

Subsequent to the review of medical records and patient/family interview, the life care planner begins the process of identifying long-term care issues and options, including considerations for aging (32). If the care planner is retained by the plaintiff, the treatment team is usually consulted and is encouraged to take an active role in development of the life care plan. In fact, if the life care planner has access to relevant treatment members and fails to communicate with them, a serious breach of professional responsibility is likely. However, it is recognized that there are cases where it is not permissible to contact treatment team members. (For additional information on this topic see 34). The life care planner acts to coordinate and communicate information to and from all members of the treatment team, patient and family. Generally, the life care planner will be the author of the document, although many people, including the patient, provide opinions and recommendations. The life care plan will identify the source of each recommendation(s), frequency, and treatment areas consistent with appropriate and reasonable care. The life care planner needs to have enough knowledge about the disability to participate in the planning process by knowing which questions to ask, who to invite to participate, how to fill in gaps of information,

and when participants' contributions are unreasonable (either excessive or deficient).

Similarly, the clinician on whom the life care planner relies needs to be competent and confident in their opinions with regard to future needs as the reliability and validity of the life care plan rests on the foundation of each individual entry. The physician or health care provider must know the patient's particular situation and the literature with regard to probable needs. For example, does a person with a brain injury really need EEGs every year to life and is there reasonable support or foundation for the recommendation? Obviously, there is a shared responsibility between the health care clinician and life care planner and the life care planner must be acutely familiar with the patient and his/her disability to know if the clinician is offering recommendations that are reasonable and resemble an accepted standard of care. For example, one of the authors met with the treating physician for a patient with tetraplegia. After a few recommendations were elicited, it was obvious the doctor was not well-versed about the long-term implications of spinal cord injury as related to future care needs. It was eventually revealed that the physician had treated only one tetraplegic patient in his career, and he happily supported the author's recommendation to refer the patient to a specialty spinal center to obtain the required information. In addition, it is the physician's or health care professional's responsibility to make sure the life care planner is qualified with which to collaborate on development of the life care plan. One way for the clinician to be sure of the life care planner's qualifications is to ask if the life care planner has completed specific training and/or achieved certification in this specialty profession (i.e., Certified Life Care Planner/CLCP).

Once an initial life care plan is developed based on adequate foundation for the entries, investigation into resources, cost research, and availability of services begins. The process of identifying resources can be a long and arduous task, involving research and personal contact with community and national resources, catalogs, and Internet databases. Upon a complete and thorough investigation, the life care plan is usually presented and reviewed by the patient/family (if clinically appropriate) and perhaps the treatment team. The plan can provide the patient, family, and treatment providers the opportunity to coordinate and execute effective care options with a clear understanding of the financial resources necessary for providing the service(s). Caveat: In the event the author of the life care plan has solicited and received written recommendations from the medical/therapeutic providers, or a consultation has been properly documented in the file, it may not be necessary to specifically send the life care plan back to the provider(s) for review. However, it is the authors' experience that having the physician or physicians who participated in development

of the plan to review and sign off or endorse the medically-based recommendations as being a reasonable plan of care can be helpful and important for case documentation.

## CLINICAL AND FORENSIC ISSUES

1. The rehabilitation expert is expected to provide an opinion in personal injury cases about what is "more probable than not" within rehabilitation certainty, as represented by the standards of the profession (7, 9, 35, 36). If a patient *might* need additional plastic surgery, then this does not represent what is more probable than not and cost for such items should not be included in the plan totals. It should not make a difference as to whether the expert is retained by the plaintiff or the defense since qualified professionals should arrive at similar conclusions if the data is appropriately analyzed (37). However, there may be occasions where there are philosophical differences or, perhaps, an attorney has provided information that is biased, and it is within the rehabilitation consultant's ethics to attempt, to the best of his or her ability, to fairly and objectively develop a plan which would accurately represent the patient's needs in order to help *resolve* litigation.
2. Replacement schedules for equipment can be dependent on a variety of conditions<sup>38</sup>. When possible, the source which supplied the product (assuming the patient already has it) should be contacted to obtain an opinion based on the individual patient. Contact with manufacturers also may be an acceptable source, although in the authors' experience, replacement schedules as promoted by the manufacturer may be less often than what it is in practical terms. Factors to consider include age, activity level, anticipated amount of use, patient's weight, and quality of product. For example, a younger individual who requires the use of a wheelchair may be very active, participate in wheelchair sports, live in a rural area that is "hard" on wheelchairs, etc., and each of these factors must be considered. Another example may be that of a patient who is 70 years of age, very sedentary, and never leaves the residential facility where he/she lives. Replacement schedules based on the above examples obviously differ for the reasons stated. An overview of basic guidelines to consider when determining replacement schedules can be reviewed in Amsterdam's chapter (38).
3. Items included in the life care plan should represent what is considered reasonable quality of care and presumes fewer complications than would otherwise be expected. The life care plan should identify potential complications based on research, patient's

history of complications, records reviewed, or expert opinion. For example, as discussed earlier in this chapter, people with ABI commonly have a higher risk of re-injury due to poor judgment and/or physical skills, among other factors. However, unless one can identify the nature of the re-injury, severity, frequency or duration, or the likelihood that re-injury has a better than 50% probability of occurrence, costs should not be included in the plan totals.

4. The life care plan generally should not include needs that are not directly related to the patient's disability. (Note: There are occasions where this rule does not apply, such as family trusts and vaccine injury fund cases). For example, a person with pre-existing diabetes would not have the cost of medication, glucose monitor, or physician visits related to diabetes included in the plan. Assuming that damages related to earnings capacity is a part of the case, costs associated with normal living expenses also would be excluded. For example, the cost of an individual's vehicle would be deducted from the cost of a handicapped van so that the plan would only include those costs associated with the need to modify the van as a result of the injury. The additional costs associated with van maintenance (only for those parts that have been modified, i.e., wheelchair lift, hand controls or other driving modifications, swivel seats, etc.), mileage to injury-related medical/therapy appointments, and increased insurance as a result of insuring a more costly, modified van would be included. Routine maintenance, fuel, etc. would not be included in the plan as the patient would have been expected to incur those costs associated with owning a regular vehicle had the injury not occurred (although an allowance for increased mileage may be added as appropriate). Similarly, the cost of home modifications as a result of the injury are reasonable to include in the plan, but the entire cost of a house is not (again, for the reason that the patient would have been expected to live somewhere had the injury not occurred). In the event the existing home is not modifiable, the value of the existing home, or the average value of a comparable home in the local community should be deducted from the value of purchasing or building an accessible home. Another example is that individuals who reside in a facility usually receive food and housing as part of the per diem cost. If a part of the patient's damages includes earning capacity, then the economist should be instructed to deduct the average yearly cost of food and housing that the patient would have expected to incur even without the injury. For patients who receive nutrition via enteral feeding, the average yearly cost of regular food should be deducted from the cost of their liquid nutrition. However, the life care planner must be cognizant of the nature of the case which may dictate what is properly included and accepted in the life care plan. As noted previously, special rules apply to litigation cases such as federal vaccine injury fund, Federal Employees Liability Act (FELA), or one of many other jurisdictions that may have special requirements.
5. For a child with a brain injury who attends public school, an individually designed educational program that includes occupational therapy, physical therapy, speech/language therapy, vision therapy, special education, and/or other resource services is available through the school at no additional cost to the family. Typically no cost for these school-based services should be included in the life care plan. However, what is defined as "educationally related" vs. "medically related" can form the basis for conflict and may determine what or whether the child receives school-based services. As suggested previously in this chapter, it may be wise to include the services of an educational consultant or expert in the life care plan to help negotiate the best school-based program. In some rare situations, a private specialty school may clinically be the best option for the patient, in which event the costs for the private specialty school will be included in the life care plan.
6. Personal injury cases in some states have collateral source rules which mean that certain patient needs, if covered by another entity, should not be a part of the life care plan. Although the life care planner must take this issue into account, the retaining attorney would know when this rule applies and should inform the expert.
7. The method for obtaining recommendations from treating professionals or other experts can take many forms. For life care planners who are retained by the plaintiff, direct contact with the treatment team is recommended. An in-person meeting with the physiatrist, for example, can assure that the life care planner has the full attention of the physician. Phone contact may also be a reasonable option, especially where distance and/or scheduling issues dictate alternate means of communication other than face-to-face. It is recommended that the life care planner take notes during such communications, then send the written notes back to the physician so that he/she can review, sign and return them to the life care planner for documentation, along with any corrections or refinements that are indicated. Another method is to send the entire life care plan to the physician(s) for review, endorsement, and signature. A third approach is to submit a letter with specific questions on which the physician can hand-write recommendations or can dictate responses typed on the doctor's letterhead. The important

factor is that written documentation verifies the medical foundation for life care plan entries.

8. For patients who require attendant care, the life care planner is expected to research agency costs (typically minimum of three sources). Some experts assert that privately hired attendants are less expensive. However, the life care planner needs to be certain that the family infrastructure for private hiring is in place. Second, the costs associated with private hire are not as low as it may seem on the surface. Costs for advertising, interviewing, hiring, bonding, background checks, training costs, back-up provision, insurance, payroll expenses, taxes, etc. are in addition to the hourly rate paid to the private caregiver (see Kitchen & Brown, 39, for additional details).
9. The concept of “medically necessary” is one which the physician and allied health professionals are familiar. In the authors’ experience, a common tenet in personal injury cases is that the injured party has a “right” to be made whole (reasonably). So, what may be “medically necessary” in Medicare may not meet the same threshold in personal injury litigation. The reader should discuss this issue with the referral source to refine the definition and be sure all necessary items are included in the plan.
10. *Qualified* life care planners are trained to conduct their assessments in the same manner (i.e., following the same methodology and procedures) regardless of who pays the bill. One test is to inquire about the percentage of plaintiff vs. defense cases on which the professional has worked. Some life care planners are noted for providing close to 100% defense work, while others are close to 100% plaintiff work. One can easily assume there is a reason. It is recognized that there is no “law” that requires life care planners to be licensed or certified (unlike physicians) and that there are some who are considered very good but who also are not certified. However, it is the authors’ opinion that certification in life care planning at least assures that the planner has knowledge about standards and procedures. As with most certifications, no competence can be assured, but minimum knowledge has been demonstrated in the testing process. Incidentally, unlike most rehabilitation related certifications, there was no “grandfathering” in the CLCP certification so all individuals who sit for the exam from the first administration in 1996 forward, has had to achieve a passing score on the test to become certified.
11. Life expectancy can be a significant factor for life care planning and controversy exists over who is qualified to render a life expectancy opinion. It is clear that a life care plan is designed to provide the needs for the patient’s life expectancy; however, for some children who are severely or significantly

impaired, they will not live to be an adult. In these and other cases of individuals with a reduced life expectancy, the age of life expectancy becomes a critical point in assessing a patient’s future. Typically, the life care planner will rely on a physician or medical expert to render the life expectancy opinion (23, 40, 41) and the life care plan needs will be adjusted accordingly. However, there are life expectancy experts who are not physicians or medical specialists who have been involved in research and have successfully been qualified in court to opine about how long a person will live (42-45). Obviously, this topic can be a battleground in forensic cases since each year that a person lives costs more. In some cases, an expert for the plaintiff may claim that a child would live to age 60 and the defense expert may opine to age 20, resulting in millions of dollars in differences. Also, in a few jurisdictions, a normal life expectancy table may be specifically required. The theory is that the defendant who is responsible for an injury that shortens one’s life should not receive “credit” for the reduction and would therefore be required to pay for damages to a normal life expectancy.

12. The Health Insurance Portability and Accountability Act of 1996 (HIPAA) will have an effect on how health care providers, life care planners, insurance companies, law firms, etc. interact with regard to medical information pertaining to an individual with a disability. The authors are beginning to see some of its effects in their own practices and some challenges that are being created as a result. Although details are beyond the scope of this chapter, many life care planners will need to sign business associate agreements with law firms and/or insurance companies and additional safeguards for “protected health information” will be required. Some life care planners have reported more difficulty interfacing with physicians and medical providers to access their patient’s medical information and research their health care needs even with a properly signed and executed information release form. As a recent example, one of the authors researched a patient’s medication costs to include in the life care plan and, as part of routine practice, asked the patient’s pharmacist for a printout of the medications and supplies. Rather than complying as had been done numerous times in the past, the pharmacist informed the life care planner that the request and information release form signed by the patient had to be sent to an outside “HIPAA compliance vendor” for review and authorization before the pharmacy would release the information. Implications of this are that the new procedure could potentially add weeks onto the research portion of the plan and

would delay obtaining the patient's actual medication history. In other instances, pharmacies have required that the patient/family personally pick up the medication history rather than send it directly to the life care planner.

## BASIC ETHICAL ISSUES

The efficacy and value of the life care plan is dependent in large part on the ethics of the person developing the plan<sup>46, 47, 48</sup>. Several common issues arise in this domain which deserve brief mention (Weed & Berens, 49, reprinted here with permission).

### Professional Preparation

The qualifications of professional rehabilitation practitioners depend on experience and academic preparation. It is imperative that one's credentials be represented accurately, and that current licensure and/or credentialing be maintained. Life care planning practitioners are held to the ethical standards of their professional discipline(s). Therefore, the life care planner should belong to a relevant organization that has ethics and/or should be certified as a life care planner (see the International Academy of Life Care Planners at [www.IALCP.com](http://www.IALCP.com) and the Commission on Health Care Certification at [www.CHCC1.com](http://www.CHCC1.com)).

### Who Is the Patient? (A.K.A. Client)

Common within the field of rehabilitation service delivery and for purposes of this chapter, the patient is the person with a disability. The life care planner is expected to provide objective, independent opinions, limited to his or her field of expertise, and demonstrate no conflict of interest. It is important that their contract for services clarifies the responsibilities and duties of the life care planner. Ultimately, the goal is to develop a document that provides for the needs of the patient over his/her lifetime in a manner that preserves quality of life, reduces potential complications, and also provides quality, appropriate, efficient and cost-effective services.

### Informed Consent

In most cases, patient consent is required for the review of confidential medical records, for patient interviews, and communication with providers of goods and services. The patient or their legal representative must understand and consent to these services. He or she is free to withdraw consent from any or all portions of services at any time. In some cases, the life care planner may act as a consultant to an insurance company or attorney, in which case, different rules may apply since direct contact may

be limited or non-existent. The life care planner must know which rules apply in the cases on which they provide services.

### Confidentiality

Protection of patient confidentiality must be maintained at all times, within legal and ethical parameters. Case managers and life care planners may release records of their work with proper authorization from the patient or his/her legal representative. Written summaries and recommendations should be addressed to the referral source who can then be responsible for distribution of copies to insurers, the patient, and service providers. Special care should be taken with the use of computerized files, electronic mail, and facsimile transmission of information in order to protect confidentiality.

### Written Reports

In personal injury litigation, it is not uncommon for the life care planner to decline to provide written opinions, probably at the request of the attorney who retained their services. Obviously, written reports represent the most common way of expressing opinions and making recommendations in all rehabilitation industries. Failure to do so in litigation related cases is inviting criticism of the life care planning process as a whole. It is the authors' opinion that the life care planner have some form of written documentation in their file.

### Use Existing Standards

Again, in personal injury litigation, certain trends are developing with regard to how life care plans are compiled. In the past, some rehabilitation consultants have chosen to use their own "private logic" when outlining future care needs. Under the Daubert<sup>50</sup> ruling (1993), it is important for the expert to develop opinions subject to published and peer reviewed methods, procedures and standards. One publication that focuses exclusively on this topic is the *Journal of Life Care Planning*, 2002, 1(1) (available through Elliott & Fitzpatrick, [www.elliottfitzpatrick.com](http://www.elliottfitzpatrick.com)). Another resource for consensus on life care planning issues is the 2000 Life Care Planning Summit Proceedings<sup>51</sup>.

## CONCLUSIONS

In general, determining lifetime future care needs for a patient with ABI can be a challenge. Oftentimes, deficits are subtle and require significant expertise to identify not only what the deficits are but strategies to assist the patient with becoming as functional and independent as possible over his/her lifetime. These cases can require a

remarkable amount of information gathering, records review, and diligent coordination among rehabilitation professionals as well as research of necessary items and services. If the evaluation is thorough, a life care plan with a reasonable estimate of financial damages can be attained and will assist in resolving the case so the patient can “get on with his or her life” (i.e., have the services in the life care plan implemented).

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**CASE STUDY\***

**Rehabilitation Plan and Vocational Worksheet Using Rapel Method and Approved by Psychiatrist and Others Involved in Client's Treatment**

Re: Losta Newron  
 Address: XXXX, Chicago, IL  
 Date of Report: 5/6/03  
 Date of Birth: 4/11/99  
 Date of Injury: 11/11/01

**Description of Injury**

Apparently, the patient was pulling on a chain when the counter to which the chain was attached fell on her. The mother states the counter weighed between 200-300 pounds and required two men to pull it off. Reportedly, the patient was unconscious and had blood coming from her ears, mouth and nose. She was diagnosed with severe closed head injury with multiple skull fractures and facial lacerations. She had a very good recovery based on the initial extent of injuries. However, several life long sequelae were expected and are outlined in the life care plan below.

**Rehabilitation Plan** (see Life Care Plan)

*Potential Complications*

Potential complications include, but are not limited to:

1. Seizure disorder.
2. Risk of re-injury due to reduced judgment, intelligence, physical skills, and visual perception.

<i>Anticipated Length of Rehabilitation Program:</i>		Through childhood and potentially lifetime.	
RECOMMENDATION	DATES	FREQUENCY	EXPECTED COST
Comprehensive neuropsychological evaluation	2004 (age 5) through 2017	Once in 2004, then yearly through 2010 (age 11), 2013, 2017 (age 18)	\$600 (2004) then \$1,000 each
Psychological	2003–2005		\$90–110 per hour
a. Individual or couples therapy for parents		Expect once per week for 6–8 mos.	
b. Family and individual client counseling	Begin 2005	Once per week for one year, twice per week from age 12 to 14, twice per week from age 16 to 18, once per week from age 18 to 21	\$90–110 per hour
Psychiatric evaluation	2003–2017	Yearly	\$75–100 each
Occupational therapy	To 2004 (age 5)	Once or twice per week	\$100 each visit
Physical therapy evaluation	Est. September 2003	Once only (also see comprehensive eval.)	\$100
Neurological evaluation	2003–2010	Yearly	\$80 each (does not include EEG or CT scans or other diagnostic studies, if needed)
Ophthalmologic evaluation for strabismus related to ABI	June 2003 to life expectancy	Yearly	\$35–55 each (does not include dilation or corrective lenses, if necessary)
Speech/language evaluation	2003 and 2004 at age 5 (included in comprehensive evaluation)	Once in 2003, 2004	\$100 (2003) 2004 cost included in comp. eval.

\*For purposes of this chapter, the below case study is in an abbreviated form.

RECOMMENDATION	DATES	FREQUENCY	EXPECTED COST
Comprehensive team evaluation (include medical, P.T., O.T., speech/language, etc.)	2004 (age 5)	Once only	\$1,800
Special education Option 1: Private school for children with disabilities. Also consider summer education or camp. Option 2: Public school system covered by the Individuals with Disabilities Education Act (IDEA). Include 13 years of learning disability consulting, 3 days per week for school year and summer school.	2003–2017	36 weeks per year (40 weeks per year if summer school)	\$10,000 per school year (recommended for maximum outcome)  4 weeks @ \$350–\$1,000 per week (summer) \$0 for public school.  \$40/hour learning disability consulting 36 weeks per year regular school or 40 weeks per year with summer school
Neurobehavior development consultant	2003–2017	3 contacts with school and patient per year to enhance educational achievement	Expect 2 hr per occasion at \$100/hr (total 6 hr per year)
Health and strength maintenance (including pool therapy, walking, and recreational activities to encourage motor coordination, perceptual training and strengthening)	2003 through entrance into school, 2004 (age 5)		No additional expected cost.
Driving evaluation	2014 (age 15)	1 X only	\$400
Vocational a. Pre-vocational evaluation	2015 (age 16)	Once only	\$600
b. Vocational evaluation	2017 (age 18)	Once only	\$600
c. Vocational counseling, guidance, placement assistance, and follow-up. (Note: Costs for job coaching and supported employment, which may be appropriate, are not included.)	2016–2019	150 hours over three years	\$65/hour
d. Post-high school education or vocational-technical training			Unknown

*Note:* This plan does not include costs associated with the patient's case management services nor her reduced ability to work outside of the home.







# Index

- A-delta fibers, 702
- A-One Evaluation, 949
- Abducens nerve (Cranial nerve VI) disorders, 536–537
- Abducens nerve palsy, 536
- Ablative stereotactic surgery, 480–481
- Abscess, brain. *See* Brain abscess
- Absorption, abnormal, 611
- Academic functioning, in neuropsychological assessment, 794–797
- Academic skills, 796, 810
- Accreditation Council of Graduate Medical Education (ACGME), 29
- Acetyl-L-carnitine, 1041
- Acetylcholine
  - cognitive impairments and, 1003–1004
  - receptors, 1026
- Achilles tendon lengthening, 648
- Actigraphy, 564
- Activated functional neuroimaging, 149–150
- Activities of daily living (ADL), 787, 947–960
  - areas of occupation, 948
  - assessment focus, 948–949
  - assessment tools, 948–949
  - best practice methods, 950–951
  - chaining technique, 953
  - client factors, 951
  - educational needs and, 957
  - electronic aids, 956
  - family dynamics and, 955
  - in functional assessment, 226
  - generalization and, 956
  - goal setting strategies, 951–952
  - as human occupations, 947–948
  - interventions for, 954–957
  - memory diaries, 954
  - occupational profile, 949–950
  - performance assessment, 950
  - personal activity improvement, 952–954
  - prompting technique, 953
  - technological devices and, 956–957
- Acute cholinergic treatment, 116–117
- Acute hospital care, 7
- Acute hydrocephalus, 584
- Acute inpatient rehabilitation, 7
- Acute repetitive seizures, 444
- Adaptive devices, motor impairment and, 953
- Adaptive plasticity, 919
- Addiction Severity Index (ASI), 799
- Addison's disease, 681
- Adducted hip deformity, 631–632
- Adelaide Activities Profile (AAP), 226
- Adenosine, 85
- Admission criteria, patient, 7
- Advanced Trauma Life Support (ATLS), 271
- Affective dysregulation, 974–976
- Affective instability, 839
- Affective lability, 853
- Age. *See also* Older adults; Pediatric perspective
  - prognosis studies and, 178–179
  - as survival factor, 251
- Aggression and agitation, 981–985
  - acute aggression
    - antipsychotics in, 981–982
    - benzodiazepines in, 982
  - chronic aggression
    - anticonvulsants in, 983
    - antidepressants in, 984
    - antipsychotics in, 982
    - benzodiazepines in, 982–983

- Aggression and agitation (*continued*)  
   $\beta$ -adrenergic receptor antagonists in, 984–985  
  buspirone in, 982  
  lithium in, 983–984  
  stimulants in, 984  
  coma and, 290  
  management of, 289–290  
  medication classes and, 290  
  nutraceuticals for, 1044–1045  
  in older adults, 325–326  
  rehabilitation process and, 827–828
- Agitated Behavior Scale, 290
- Agitation. *See* Aggression and agitation
- Airbag use, 60–61, 73
- Akathisia, 470, 981
- Albee, Fred, 15
- Alcohol, seizure risk and, 444
- Alcohol abuse, 69–72, 291–292, 1108–1110. *See also*  
  Substance abuse
- Alcohol Use Disorders Identification Test (AUDIT),  
  1108
- Alexander technique, 1076
- Allen Cognitive Test, 949
- Allodynia, 699
- Alprostadil, 685
- Alternate decision makers, 1214–1217
- Alternative medicine. *See* Complementary and  
  alternative medicine
- Alternative movement therapies, 1076
- Alzheimer's disease, 328, 359–360, 850
- Amantadine, 530, 978, 1001, 1010, 1028
- Amantadine hydrochloride, 433
- Ambient visual processing, 515, 516
- Amenorrhea, 690
- American Academy of Certified Brain Injury Specialists  
  (AACBIS), 5, 31–32
- American Board of Physical Medicine &  
  Rehabilitation (ABPMR), 29
- Americans with Disabilities Act (ADA), 17
- Amitriptyline, 970, 1011
- Amnesia, 784  
  in mild traumatic brain injury, 342–343  
  retrograde, 410  
  sports-related concussion and, 409–410
- Amphetamines, 1031
- Analgesic rebound headaches, 716
- Analgesics, in pain management, 704
- Androgen substitution, 685
- Andropause, 685
- Aneurysms, traumatic, 592
- Anosmia, 325
- Anosognosia, 781–782, 1187  
  impact of, 781–782  
  mechanisms of, 782  
  treatment of, 782
- Anterior commissure, 218
- Anterior pituitary dysfunction, 681
- Anticonvulsant drugs  
  in chronic aggression, 983  
  in neuropathic pain states, 704–706  
  reproductive issues and, 690  
  after TBI, 987–988
- Antidepressant drugs, 967–972  
  in affective dysregulation, 975  
  in chronic aggression, 984  
  drug–drug interactions with, 972–973  
  methylphenidate, 972  
  monoamine oxidase inhibitors, 971–972  
  in neuropathic pain states, 704–706  
  novel antidepressants, 971  
  seizures and, 972  
  selective serotonin reuptake inhibitors, 967–970  
  sexual dysfunction and, 686  
  sleep disturbances and, 568  
  tricyclic and tetracyclic agents, 970–971
- Antidiuretic hormone, 679
- Antiepileptic drugs, 706  
  adverse effects and, 457  
  clinical trials and guidelines, 454–455  
  GABA pathways and, 1032  
  sleep disturbances and, 568  
  substitution, 457–458  
  therapy duration, 458  
  treatment and selection of, 456–457
- Antihistamines, sleep disturbances and, 568
- Antihypertensive drugs, 683–684
- Antioxidant disruption, immobility and, 607–608
- Antipsychotic drugs, 979–980  
  in acute aggression, 981–982  
  atypical, 847, 980  
  in chronic aggression, 982  
  dopamine blockade and, 1027  
  sleep disturbances and, 569  
  special considerations, 980  
  typical antipsychotics, 979–980
- Antisiphon devices, 590
- Anxiety disorders, 847–849, 976–977  
  benzodiazepines in, 976–977  
  buspirone in, 977  
  generalized anxiety disorder, 847  
  obsessive-compulsive disorder, 848  
  post-concussive disorder and, 385–386  
  post-traumatic stress disorder, 848–849  
  selective serotonin reuptake inhibitors in, 976
- Apathy, 839–840, 977–979  
  amantadine in, 978  
  bromocriptine in, 978–979  
  dextroamphetamine in, 979  
  L-dopa/carbidopa in, 979  
  methylphenidate in, 979

- Apathy Evaluation Scale, 852  
 Aphasia, 896–897  
 Apolipoprotein E4 (APOE-4), 188, 253, 328  
 Apomorphine, 685  
 Apoptosis cascades, 85–87  
 Apoptosis-inducing factor (AIF), 86  
 Apparent diffusion coefficient (ADC), 146  
 Apraxia, motor impairment and, 953  
 Arginine, 666–667  
 Aripiprazole, 847  
 Aromatherapy, 1065  
 Arousal system, 995–996  
 Articulatory function, 870  
 Ascending reticular activating system (ARAS), 526  
 Ashworth Scale, 939  
 Aspiration, 748  
 Assent, in brain injury rehabilitation, 1217  
 Assessment, 284–294
  - agitation and, 289–290
  - bladder and bowel function, 293
  - cardiovascular autonomic disorders and, 290–291
  - in disorders of consciousness, 436
  - dystonia and, 294
  - early rehabilitation intervention and, 286
  - fever and, 292–293
  - management of minimally responsive patient, 286–287
  - muscle overactivity and, 294
  - posttraumatic amnesia and, 287–289
  - prognosis, 284–286
  - residual impairments and, 284
  - respiratory disorders and, 291–292
  - spasticity and, 294
  - swallowing and nutrition and, 293–294
 Assessment of Intelligibility of Dysarthric Speech (ASSIDS), 868  
 Assistive technology devices (ATD), 956  
 Associated neurological impairments, 854  
 Ataxic dysarthria, 867  
 Athetosis, 470  
 Atomoxetine, 530  
 Atrophy, immobility and, 607  
 Attention
  - concentration tests, 796
  - deficit remediation, 767–769
  - deficits, 780–781
  - electrophysiological studies of, 996
  - in older adults, 325
  - process of, 996–997
  - remediation and, 810
  - spatial attention, 996
  - visuospatial function and, 996
 Attention deficit hyperactivity disorder (ADHD), 1001  
 Attention process training (APT), 767–768  
 Attorneys, in TBI litigation, 1151–1152  
 Attribution bias, 1185–1186  
 Autogenic training, 1066  
 Autonomic dysfunction, 290–291  
 Awareness deficits, 839  
 Axial proton density magnetic resonance, 217  
 Axonal injury, 88, 1024  
 Baclofen, 635, 1032  
 Balance and dizziness, 491–510
  - assessment tools, 496–498
  - benign paroxysmal positional vertigo, 493, 500–501
  - central nervous system causes, 496
  - central vestibular compensation process, 493
  - disorders of, 940
  - electronystamography in, 498
  - exercise guidelines, 508
  - falls and, 64–65
  - gaze instability, 501–503
  - immobility and, 611
  - laboratory studies and, 498
  - labyrinthine concussion and, 493–494
  - motion sensitivity and, 503–505
  - neurotologic history and, 497
  - ocular motor control and, 492
  - office examination and, 497–498
  - perceptions of motion and, 492
  - perilymphatic fistula and, 495–496
  - peripheral vestibular disorders, 493
  - postural and motor system control and, 492–493
  - postural control assessment and, 498
  - postural instability and, 505–508
  - rehabilitation therapy programs and, 499–508
  - rotary chair testing and, 498
  - sources of complaints after TBI, 493–496
  - sports-related concussion and, 410
  - temporal bone fractures and, 494–495
  - treatment options and, 498–499
  - vestibular and balance rehabilitation outcomes, 508
 Ballism
  - classification of, 470
  - diagnosis of, 476–477
  - treatment of, 484
 Barbiturates, 663  
 Barium swallow, 889–901  
 Barthel Index, 238, 924, 949  
 Basal forebrain damage, 218  
 Basal ganglia, posttraumatic fatigue and, 526–527  
 Basilar skull fractures, 578, 580  
 Battery for Health Improvement, 728–729  
 Bcl-2, 87  
 Beck Anxiety Inventory (BAI), 731  
 Beck Depression Inventory (BDI), 564, 731, 798, 852, 967, 968

- Bedrest. *See* Immobility
- Bedside examination, in disorders of consciousness, 427–429
- Behavioral approach  
to dysarthric speech rehabilitation, 870–871  
to linguistic rehabilitation, 877
- Behavioral assessment  
of cognition, 818  
in disorders of consciousness, 429–430  
of emotional status, 816–818  
introduction to, 816  
measures of, 852  
surveys of, 852
- Behavioral disturbances, nutraceuticals for, 1042–1044
- Behavioral function, posttraumatic seizures and, 449
- Behavioral interventions, 755, 818–825
- Behavioral management, in neuropsychological treatment, 809
- Behavioral metaphors, 855
- Behavioral observations, in neuropsychological assessment, 794–795
- Behavioral problems  
expertise in, 7  
pediatric patient, 308–309
- Behavioral treatment strategies, 937–938  
high-level cognitive management, 938  
low-level cognitive management, 937–938  
mid-level cognitive management, 938
- Benedikt's syndrome, 473
- Benign paroxysmal positioning vertigo (BPPV), 493, 500–501, 940
- Benzodiazepines  
in acute aggression, 982  
in anxiety disorders, 976–977  
in chronic aggression, 982–983  
GABA pathways and, 1032
- Berg balance scale, 939
- Bi-Aura therapy, 1069
- Bielchowsky's Head Tilting test, 518
- Bilateral vestibular hypofunction (BVH), 502
- Bimodal vision process, 512–514
- Binasal occluders, 515
- Binocular function assessment, 517–519
- Binocular intervention, 524–526
- Binocularity, 514–515
- Biochemical pharmacology of wakefulness, 562
- Bioenergetics, 710
- Biofeedback, 1067  
for chronic pain, 737  
for sleep disturbances, 566
- Biopsychosocial assessment, pain, 727–732
- Bladder function, 293, 323–324
- Bladder training, 749–750
- Bloody stool, 659
- Blurred vision. *See* Visual dysfunction
- Body weight maintenance, 668–669
- Body weight support, 942–943
- Bone density loss, 606–607
- Bone mineral density, 65
- Botulinum neurotoxin, 636–640
- Bowel function, 293, 324
- Bowel regimens, 669
- Boxing injuries, 65–66
- Bradykinesia, 470
- Braille, Louis, 15
- Brain abscess, 581–583  
clinical presentation, 581–582  
organisms and treatment, 582–583  
risk factors, 581–582  
stages and imaging, 582
- Brain contusions, static neuroimaging in, 134–136
- Brain edema, 269
- Brain Injury Association of America (BIAA), 17, 1088
- Brain injury depth, as factor in survival, 252
- Brain plasticity and recovery, 914–915
- Brain structures, comparing volumes of, 205
- Brainstem auditory evoked potentials (BAEP), 158–159
- Brainstem structures, sexuality and, 675–676
- Braintree Neurologic Stages of Recovery, 11
- Branched motor pathway, 530
- BRIEF-A, 852
- Brief Michigan Alcoholism Screening Test (B-MAST), 799
- Brief Symptom Inventory (BSI), 798
- Bright light therapy, 565
- British Columbia Postconcussion Symptom Inventory, 378–379, 404–405
- Bromocriptine, 433, 978–979, 1009–1010, 1028
- Bruit hydro-aérique, 580
- Brunnstrom approach, 939
- Bruxism, 560
- Bupropion, 971
- Buspirone, 977, 982
- C-fibers, 702
- Caffeine, sleep disturbances and, 563
- CAGE test, 799
- Calcium channel blockers, 110
- Calendar year, as factor in survival, 251–252
- Caloric requirements, 664–665
- Caloric Stimulation Testing, 540
- Canadian Occupational Performance Measure (COPM), 233, 949
- Canalith Repositioning Maneuver, 495
- Capacity  
in functional assessment, 228  
issues regarding, 1152  
in older adults, 326

- Capsaicin, 706  
 Car seat use, 73  
 Carbamazepine, 706, 876, 973, 987, 988  
 Carbidopa/L-dopa, 1010–1011  
 Cardiovascular abnormalities, 748  
 Cardiovascular autonomic disorders, 290–291  
 Cardiovascular system, immobility effects on, 608–610  
 Care, quality of  
   as factor in survival, 253  
   life expectancy and, 255–256  
 Care system development, 4–5  
 Career development, 1136–1138  
 Carotid cavernous fistula, 592–593  
 Catastrophic reactions, rehabilitation process and, 828–829  
 Catecholamine agonists, functional recovery and, 114–115  
 Catecholaminergic agents, in affective dysregulation, 975  
 Catecholaminergic system changes, 836–837  
 Catecholamines, cognitive impairments and, 1001–1002  
 Catechol-O-methyltransferase (COMT), 1001–1002  
 CDP-choline, 1015–1016, 1038–1039  
 Cell signaling abnormalities, in neuronal death, 87–88  
 Cellular swelling, 89–90  
 Center on Outcome Measurement in Brain Injury, 237  
 Centers for Medicare and Medicaid Services (CMS), 235  
 Central nervous system  
   balance problems and dizziness and, 496  
   lesions, 285  
   reorganization, 100–102  
 Central nystagmus, 539  
 Central occlusion, 526  
 Central pain syndromes, 717–718  
 Central sensitization, 699  
 Central vertigo, 539  
 Central vestibular compensation process, 493  
 Cephalgia, 701  
 Cerebral blood flow, 270, 276  
 Cerebral contusions, 266  
 Cerebral edema, 138–140  
 Cerebral perfusion pressure, 270–271  
 Cerebral salt wasting, 662  
 Cerebral swelling, 88–90  
 Cerebrospinal fluid  
   fistulas, 578–580  
   meningitis risk and, 579–580  
   otorrhea, 580  
   pneumocephalus, 580  
   rhinorrhea, 578–579  
   tap test, 586  
 Cervical arterial trauma, 592  
 Cervical injuries, post-concussive disorder and, 380–381  
 Cervical-ocular reflex, 502  
 Cervicalgia, 701  
 Cervicogenic headache, 713–714  
 Chaining technique, 953  
 Chemical messengers, 675  
 Chemical senses, 786  
 Child abuse, 72–73  
 Children. *See* Pediatric patient  
 Chinese medicine. *See* Traditional Chinese medicine (TCM)  
 Choline, 1037  
 Cholinergic dysfunction, 1003–1004  
 Cholinergic system  
   acute injury in, 1026  
   changes in, 837  
   controversy regarding, 1026–1027  
   recovery in, 1026  
 Cholinesterase inhibitors, 1012–1015  
   in apathetic states, 979  
   in clinical practice, 1015  
 Chorea  
   classification of, 470  
   diagnosis of, 476–477  
   treatment of, 484  
 Chronic communicating hydrocephalus. *See* Hydrocephalus  
 Chronic daily headache (CDH), 716  
 Chronic pain, post-concussive disorder and, 384  
 Chronic Pain Acceptance Questionnaire (CPAQ), 729  
 Chronic Pain Coping Inventory (CPCI), 729  
 Chronotherapy, 565  
 Circulatory system diseases, 249  
 Cisternography, in hydrocephalus, 585  
 Claude's syndrome, 473  
 Clenched fist deformity, 630  
 Client factors, 951  
 Clinical continuum, essential components of, 4–9  
 Clinical interviews, in neuropsychological assessment, 794  
 Clinical office practices, 1170–1171  
 Clinical pathways, critical care nursing management and, 746  
 Clinical presentation, 271–272  
 Clinical trials, 35–37  
 Clinico-legal examinations, 1171–1181. *See also*  
   Ethical issues; Medicolegal issues  
   addressing ethical violations, 1180–1181  
   admissibility of expert witness testimony, 1179  
   assessment procedure selection, 1175–1176  
   confidentiality issues, 1173  
   court-hired experts, 1179  
   disclaimer statements, 1178



- Clinico-legal examinations (*continued*)  
 documentation review, 1176–1177  
 drafts and final reports, 1177–1178  
 expert witnesses, 1178–1179  
 findings disclosure, 1177  
 ground rules communication to examinee, 1172  
 ground rules establishment, 1171–1172  
 informed consent, 1173  
 monitoring bias, 1180  
 perceived control and quality assurance, 1173  
 record completeness, 1177  
 reporting critical components, 1176  
 response bias and, 1172–1173  
 testing delegation, 1176  
 third party observers, 1174–1175
- Clonidine, 987
- Clonus, 617–618
- Clozapine, 847, 980
- Co-contraction, muscle, 618
- Coenzyme Q10, 1046
- Cogniphobia Scale (C-Scale), 729
- Cognition  
 assessment of, 818  
 bedrest and, 610–611  
 bedside measures of, 852  
 deficits in pediatric patients, 306  
 function deficits and survival, 251–252  
 nutraceuticals for, 1037–1042  
 posttraumatic seizures and, 449  
 processing in pediatric patient, 308
- Cognitive-behavioral treatments, for chronic pain, 737
- Cognitive-communication deficits, 895–910  
 conversation analysis, 904  
 conversational discourse, 902–907  
 diffuse axonal damage and, 897  
 discourse analysis and, 897–898  
 focal left hemisphere damage and, 896  
 focal right hemisphere damage and, 896–897  
 focal subcortical damage and, 897  
 language disorders and site of lesion, 895–897  
 macrolinguistic analyses, 900–901  
 measurement of informativeness, 901  
 multilinguistic analyses, 899–900  
 narrative discourse, 899–902, 906–907  
 pragmatic rating scales, 904–905  
 social information processing, 905  
 systemic functional linguistics and, 903–904
- Cognitive Coping Strategies Inventory, 730
- Cognitive functioning, in neuropsychological assessment, 794–797
- Cognitive impairment, 779–790. *See also* Cognitive impairment pharmacotherapy  
 anosognosia, 781–782  
 chemical senses, 786  
 confabulations and delusions, 785  
 effects of, 854  
 executive functions, 786–788  
 information processing and attention, 780–781, 784–785  
 intellectual functioning, 782–783  
 memory, 783–785  
 neuropsychological evaluation, 779–780  
 post traumatic amnesia, 784  
 social cognition and behavior, 878–788  
 spatial cognition, 785–786
- Cognitive impairment pharmacotherapy  
 acetylcholine and, 1003–1004  
 amantadine and, 1010  
 arousal and, 995–996  
 attention and, 996–997  
 bromocriptine and, 1009–1010  
 carbidopa/L-dopa and, 1010–1011  
 catecholamines and, 1001–1002  
 CDP-choline and, 1015–1016  
 cholinesterase inhibitors and, 1012–1015  
 complex cognition and, 999  
 glutamate and, 1000–1001  
 language and, 997–998  
 memory and, 997  
 modanfinil and, 1011  
 neurobiological bases, 1000–1004  
 praxis and, 999  
 prosody and, 998  
 psychostimulants and, 1006–1009  
 serotonin and, 1002–1003
- Cognitive rehabilitation, 765–778  
 attention deficits and, 767–769  
 communication deficits and, 772–773  
 executive functioning deficits and, 771–772  
 functional skills training, 766  
 intensive-holistic rehabilitation, 773–774  
 memory deficits and, 769–771  
 neurocognitive function recovery, 765–767  
 process-specific remediation, 766
- Cognitive remediation, in neuropsychological therapy, 809
- Cognitive syndromes, 838
- Coldness, 986
- Coma  
 definition of, 424  
 depth of and prognosis, 285  
 duration of and prognosis, 285  
 length of and prognosis, 177–178  
 pregnancy and, 690  
 rehabilitation from, 287
- Coma/Near Coma Scale, 287, 429
- Coma to Community model, 22–23
- Commission on Accreditation of Rehabilitation Facilities (CARF), 4, 5, 17, 28, 235, 1085

- Communicating hydrocephalus, 144
- Communication deficits, 772–773. *See also*  
Cognitive-communication deficits
- Communication of prognosis, 181–186  
barriers to communication, 182  
ensuring understanding, 183  
fostering hope, 186  
guidelines for, 182–186  
practical suggestions, 185–186  
presenting statistical information, 183–185  
process optimization, 186
- Communication skills, pediatric patient, 309
- Community Integration Questionnaire (CIQ), 35, 227, 239–240
- Community reentry services, 1085–1104  
determining need for, 1100–1101  
driving after TBI, 1091–1097  
education and training, 1101–1102  
efficacy of community based programs, 1088–1089  
family adjustment, 1090  
funding for, 1089  
limited community mobility, 1091–1098  
medical consultation, 1098–1100  
medical management, 1098–1100  
need for, 1085–1086  
paratransit services, 1097–1098  
physician role in, 1098–1102  
prevalent issues, 1089–1098  
program design and treatment models, 1087–1088  
public transportation use, 1097–1098  
social isolation, 1091  
treatment in real life contexts, 1089
- Comorbidities, common, 804
- Compartmental impairments, 999
- Compensation, in motor behavior, 919
- Compensatory approach, to linguistic rehabilitation, 877, 878
- Compensatory strategies, 953
- Compensatory treatment, in dysphagia, 891
- Competency, 326, 1152. *See also* Decision making capacity
- Complementary and alternative medicine, 1061–1082  
alternative movement therapies, 1076  
aromatherapy, 1065  
clinical trials and, 1063  
craniosacral manipulation, 1070–1071  
definition of, 1061–1062  
electrical and magnetic therapies, 1072–1076  
electroencephalographic biofeedback, 1067–1069  
energy based therapies, 1069–1070  
homeopathy, 1063–1065  
hyperbaric oxygen therapy, 1076–1078  
naturopathy, 1063–1065  
physician attitude towards, 1062  
relaxation therapies, 1065–1067  
spiritual healing, 1071–1072
- Complex cognition functions, 999
- Complex partial seizures, 444
- Complex regional pain syndrome, 718
- Compression stockings, 748
- Computed tomography (CT)  
in brain contusions, 134–136  
in cerebral edema, 138–140  
day-of-injury (DOI), 208  
descriptive abnormality categories, 212  
in dystonia, 477  
in epidural collections, 141–142  
in herniation syndromes, 138  
in hydrocephalus, 144, 584–585  
imaging techniques, 130–131  
predicting outcome and, 144–147  
prognosis studies, 176–177  
in shearing injuries, 136–138  
in sports-related concussion, 411–412  
in subarachnoid hemorrhage, 142–143  
in subdural collections, 140–141  
in tremors, 473–474
- Computer adaptive testing (CAT), 229
- Concussion, 268. *See also* Headaches; Sports-related concussions  
definition of, 407–408  
grading scales, 415–416  
labyrinthine, 493–494
- Concussion headache, 410
- Conditioned Avoidance Pain Related Disability (CAPRD), 1186
- Conductive hearing loss, 538
- Confabulations, 785
- Conferences, international, 23
- Confidentiality, 1173, 1236
- Confusion, sports-related concussion and, 409
- Constipation, 611, 659–660
- Constraint-induced movement therapy, 922–924, 941–943
- Construct validity, of functional assessment instruments, 231–232
- Contextual interference effect, 934
- Continence, in older adults, 323–324
- Contingency management, in behavioral interventions, 818–822
- Continuous electroencephalography (EEG), 276
- Continuous quality improvement (CQI), 235
- Contraception, 691
- Contractures, 295
- Conversation analysis, 904–905
- Conversational discourse, 902–906  
conversation analysis, 904  
exchange structure analysis, 903–904



- Conversational discourse (*continued*)  
  impairments, 907  
  pragmatic rating scales, 904–905  
  response appropriateness, 902–903  
  social information processing, 905  
  systematic functional linguistics, 903–904  
  topic management, 903
- Conversion disorder, 805
- Coping strategies, 1028. *See also* Interventions
- Coping Strategies Questionnaire, 730
- Cortical activation, 303
- Cortical structures, anatomical alterations after injury, 920–921
- Cortical tissue, plasticity of function and, 106
- Corticosteroids, in pain management, 704
- Cost projections, in life care planning, 1231
- Coulter, John, 16
- Counseling, interventions and, 823–825
- Cover test, 518
- Craig Handicap Assessment and Reporting Technique (CHART), 35, 226, 239
- Cranial electrotherapy stimulation, 565–566
- Cranial nerve disorders, 529–544  
  abducens nerve and, 536–537  
  components of cranial nerves, 531  
  examination and function, 530  
  facial nerve and, 537–538  
  glossopharyngeal nerve and, 541  
  hypoglossal nerve and, 542  
  oculomotor nerve and, 534–535  
  olfactory nerve and, 531–533  
  optic nerve and, 533–534  
  sensory pathways and, 530  
  somatic and brachial motor pathways and, 530  
  spinal accessory nerve and, 542  
  trigeminal nerve and, 535–536  
  trochlear nerve and, 535  
  vagus nerve and, 541–542  
  vestibulocochlear nerve and, 538–541  
  visceral motor pathways and, 530–531
- Cranial rhythmic impulse, 1071
- Cranial succession splash, 580
- Cranial trauma, 381–384
- Craniectomy, 583
- Cranioplasty, 583
- Craniosacral manipulation, 1070–1071
- Creatine, 1046
- Criminal activity, 1107
- Critical care, 275–276
- Crocodile tears, 538
- Cryotherapy, 294
- Cultural differences, 1186
- Culturally sensitive interventions, 1027
- Curcumin, 1046
- Cycling injuries, 65
- Dantrolene sodium, 634
- Data availability, 46–47
- Data sources, 48
- Day-of-injury (DOI) computed tomography, 208, 211–214
- Decannulation, 292
- Decision making capacity, 1205–1222  
  alternative decision-maker choice, 1214–1217  
  assent and dissent, 1217  
  assessment questions to ask, 1209  
  balancing autonomy with beneficence, 1206  
  components of, 1208  
  hypoemotionality and, 1213  
  Karen Ann Quinlan case, 1218  
  key principles, 1206–1208  
  Michael Martin case, 1219  
  model limitations, 1211–1214  
  Nancy Beth Cruzan case, 1218–1219  
  neuropsychological testing and, 1210–1211  
  relevant information patient must understand, 1208  
  Robert Wendland case, 1219  
  standard assessment model, 1208–1210  
  surrogate decision making, 1218–1220  
  Terri Schiavo case, 1220  
  withdrawal or withholding life-sustaining treatment, 1218–1220
- Declarative memory disturbances, 997
- Deconditioning, 941
- Deep brain stimulation (DBS), 160, 433, 481, 484
- Deep venous thrombosis, 275, 294–295, 322
- Deep venous thrombosis/pulmonary embolus (DVT/PE), 307
- Delayed gastric emptying, 658–659
- Delta sleep-inducing peptide (DSIP), 562–563
- Delusions, 785
- Dementia, 325, 850–851
- Demonstrative evidence in TBI cases, 1159–1160
- Depressed skull fractures, 578
- Depression, 842–844. *See also* Antidepressants  
  as long-term problem, 279  
  mild traumatic brain injury and, 351, 357–358  
  neural circuitry of, 843  
  neurochemistry of, 843  
  nutraceuticals for, 1044–1045  
  in older adults, 326  
  post-concussive disorder and, 385–386  
  post-traumatic fatigue and, 528  
  rehabilitation process and, 828–829  
  suicide and, 69  
  treatment of, 843–844
- Desensitization model for chronic pain, 736
- Desipramine, 970
- Desperation-induced malingering, 1186
- Dextroamphetamine, 530, 979, 1007–1008, 1008–1009

- Diagnosis threat, 389–390, 1186
- Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), 377–379, 842
- Diagnostic testing, in life care planning, 1226
- Diarrhea, 293, 659–660
- Diaschisis, 102–103, 919
- Diazepam, 634–635, 1032
- Diet change, swallowing disorders and, 892–893
- Differential diagnosis in neuropsychological assessment, 803–805
- Differential reinforcement of incompatible behavior (DRI), 821
- Differential reinforcement of low-rate behavior (DRL), 821
- Differential reinforcement of other behavior (DRO), 821
- Diffuse axonal damage, 897
- Diffuse brain injury, 206–210
- Diffuse injury, 10–12
- Diffusion tensor imaging (DTI), 202
- Diffusion-weighted MRI, 139, 146
- Diplopia, 524–526, 535
- Direct visualization ophthalmoscope, 534
- Disability evaluation. *See* Impairment and disability evaluation; Response bias
- Disability incidence, recent epidemiological findings, 51–52
- Disability policy in United States, 1134–1136
- Disability prevalence, recent epidemiological findings, 52
- Disability Rating Scale (DRS), 35, 226, 241, 277–278
- Disablement model, 931–933
- Discourse, 897–908
  - analysis of, 897–898
  - conversational discourse, 902–906
  - narrative discourse, 899–902
- Disinhibition, 687
- Disorders of consciousness (DOC), 423–440
  - assessment strategies, 436
  - bedside examination, 427–429
  - clinical assessment, 427–430
  - coma defined, 424
  - definitions regarding, 423–425
  - diagnostic criteria, 423–425
  - ethical considerations, 437
  - functional neuroimaging studies, 425–427
  - future directions, 437–438
  - individualized behavioral assessment, 429–430
  - minimally conscious state defined, 424–425
  - neuropathology, 425
  - outcome following minimally conscious state, 435–436
  - outcome following vegetative state, 434–435
  - prognosis, 434–436
  - standardized rating scales, 426
  - systematic approach to examination, 428
  - treatment efficacy, 430–433
  - treatment strategies, 436–437
  - treatment types, 430
  - vegetative state defined, 424
- Dissection, 592
- Dissent, in brain injury rehabilitation, 1217
- Divergence paralysis, 518
- Dix, Dorothea, 15
- Dix-Hallpike Positional Test, 495, 539–540
- Dizziness. *See* Balance and dizziness
- Dizziness Handicap Inventory, 497
- Do not resuscitate laws, 1153–1155
- Domperidone, 659
- Donepezil, 1013–1015
- Dopamine enhancing medications, 1028
- Dopamine pathways
  - acute injury in, 1027
  - controversy regarding, 1027–1028
  - recovery in, 1027
- Dopaminergic agents, sexual dysfunction and, 685
- Driving, 1091–1097
  - assessment of, 1092, 1096–1097
  - epilepsy and, 1093–1095
  - issues in older adults, 327
  - neurocognitive driving test (NDT), 1095
- Drug abuse. *See* Substance abuse
- Drugs, seizure risk and, 444
- Drunk driving, 71
- Dynamic Gait Index (DGI), 940
- Dysarthria, 866–868
  - articulatory function, 870
  - ataxic dysarthria, 867
  - behavioral approaches to, 870–871
  - case reports, 871–873
  - childhood dysarthria, 867–868
  - flaccid dysarthria, 867
  - hyperkinetic dysarthria, 866–867
  - hypokinetic dysarthria, 866–867
  - instrumental approaches to, 871
  - instrumental assessment, 869
  - laryngeal function, 869
  - mixed dysarthria, 867
  - multisystem approach to, 874–875
  - perceptual assessment, 868
  - prosthetic/surgical approaches to, 871
  - respiratory function, 869–870
  - spastic dysarthria, 866
  - treatment approaches, 870–871
  - velopharyngeal function, 870
- Dysautonomic headache, 716
- Dysexecutive syndromes, 838–840
- Dysphagia
  - compensatory treatment, 891

- Dysphagia (*continued*)  
diet change and, 892–893  
enhancing sensory input, 891  
evaluation of, 888–889  
exercise programs and, 892  
in rehabilitation environment, 668  
safety and, 953  
swallow maneuvers and, 891–892  
treatment/management of, 891–893
- Dysrhythmias, 291
- Dyssomnia. *See* Sleep disturbances
- Dystonia, 294  
classification of, 470  
diagnosis of, 475–476  
medical treatment, 484  
spastic, 649–620  
surgical treatment, 484
- Early posttraumatic seizures, 275
- Easy Street, 955
- Ecological validity, of functional assessment  
instruments, 231–232
- Economic costs, 52–53, 58
- Ectopic impulse generation, 699
- Edema, brain, 269
- Education, 1141  
community re-entry programs and, 1101–1102  
as factor in survival, 252  
injury prevention programs and, 60  
in life care planning, 1226, 1228  
in neuropsychological treatment, 807–808
- Effortful swallow, 891
- Elbow deformity, 626–627
- Elbow rehabilitation, 642–643
- Elderly. *See* Older adults
- Electrical and magnetic therapies, 1072–1076
- Electrical stimulation, 1073
- Electro-crystal therapy, 1075
- Electro-homeopathy, 1075–1076
- Electro-Oculograms (EOG), 521
- Electrocardiographic abnormalities, 291
- Electroconvulsive therapy (ECT), 972
- Electroencephalography (EEG), 159–160, 276  
in biofeedback, 1067–1069  
conventional, 159–160  
in post-traumatic seizures, 453–454, 455–456  
quantitative, 160  
sports-related concussion and, 412
- Electromagnetic articulography (EMA), 870
- Electronic aids to daily living (EADL), 956
- Electronystagmography (ENG), 497, 498
- Electropalatography (EPG), 870
- Electrophysiological assessment techniques, 157–166  
brainstem auditory evoked potentials, 158–159  
electroencephalograms, 159–160  
event-related potentials, 161–162  
pain-related potential (P250), 160–161  
somatosensory evoked potentials, 157–158
- Electrophysiological testing, 520–521
- Elms, Edgar James, 15
- Emergency medical services, 4–5
- Emotional incontinence, 975
- Emotional status, assessment of, 816–818
- Employer negotiation strategies, 1139–1141
- Empyema, subdural, 581
- Endocrine system, immobility effects on, 611
- Endogenous neuroprotectants, 85
- Energy-based therapies, 1069–1070
- Enteral feeding, 294
- Enteral nutrition support, 665–666
- Environmental enrichment, 117–118
- Environmental interventions, 746–755, 823
- Epidemiology, 45–56  
data availability, 46–47  
definitions, 45–46  
incidence and prevalence, 46  
outcome, 46  
severity, 46  
traumatic brain injury, 45–46  
findings application to public health, 53  
hospitalizations and deaths- other countries, 48–49  
methodological issues, 46–48  
of movement disorders, 470–471  
published population-based studies, 48–53  
quality of data sources, 48  
recent epidemiological finding- United States, 50–52  
trends in TBI incidence- United States, 48
- Epidural collections, static neuroimaging in, 141–142
- Epidural hematoma, 595
- Epidural hemorrhages, 267, 272
- Epilepsy. *See also* Antiepileptic drugs; Posttraumatic seizures and epilepsy  
as cause of death after TBI, 248  
driving and, 1093–1095  
as factor in survival, 251–252
- Epileptic focus, surgical resection of, 458–459
- Epileptic seizure classification, 443
- Epileptogenesis, posttraumatic, 450–451  
ferric chloride model, 450–451  
kindling models, 451
- Epworth Sleepiness Scale, 564
- Equinovarus foot deformity, 633–634
- Equipotentiality, 100–102
- Erosions, gastric, 658
- Errorless learning in interventions, 822
- Erythromycin, 659
- Esotropia, 536
- Estrogen, 681

- Ethanol, 113
- Ethical considerations, in disorders of consciousness, 437
- Ethical issues, 1163–1182. *See also* Clinico-legal examinations
- autonomy, 1164–1165
  - avoiding ethical misconduct, 1165–1170
  - beneficence, 1164–1165
  - biomedical ethics and TBI, 1164–1165
  - ethical clinical office practices, 1170–1171
  - expert witness testimony, 1169–1171
  - justice, 1164–1165
  - material contribution to case resolution, 1167
  - neutrality and selectivity, 1170–1171
  - neutrality and sphere of expertise, 1166–1167
  - non-maleficence, 1164–1165
  - practice paradigm shift, 1164
  - proactivity and, 1165
  - professional role distinctions, 1168–1169
  - qualifications and expertise maintenance, 1166
  - relational conflict issues, 1167–1168
- Evaluation, patient, 682–684
- laboratory tests, 684
  - medical history, 682
  - medication review, 683–684
  - neurophysiologic evaluation, 684
  - physical examination, 683
  - psychological evaluation, 682–683
  - questionnaires, 683
  - vascular evaluation, 684
- Event-related potentials (ERP), 160–162, 412
- Exaggeration, post-concussive disorder and, 390–392
- Examinee response bias, 1184–1185
- Exchange structure analysis, 903–904
- Excitatory amino acids, 268–269
- Excitotoxic cascade, 1027
- Excitotoxicity, 84–85, 109–110
- Excitotoxins, inhibiting release of, 109
- Executive function, 771–773, 786–788, 999
- Exercise, 710, 941
- principles of, 935–936
  - task-specific training, 935
  - training intensity, 935–936
- Exercise programs, swallowing disorders and, 892
- Exogenous growth factors, 111
- Expert witnesses, 1158–1159, 1171, 1178–1179
- Exposure keratitis, 538
- Extensor spasms, 618–619
- Extinction, 820
- Extracellular signaling, of apoptosis, 87
- Face validity, of functional assessment instruments, 231
- FACES Scale, 728
- Facial nerve (Cranial nerve VII) disorders, 537–538
- Facial nerve palsy, 537
- Facility care determination, in life care planning, 1227
- Factitious disorders, 1186
- Fallopian canal lesions, 537
- Falls, 756–757
- injury from, 63–65
  - restraints for prevention, 756–757
  - siderails for prevention, 757
- Family
- activities of daily living and, 955
  - assessment, 801
  - cognitive-behavioral intervention for, 1021–1028
  - community re-entry and, 1090
  - counseling for swallowing problems, 888
  - critical care nursing management and, 746, 753–754
  - impact of TBI on, 1118
  - injury-related stress and, 1118
  - interventions in neuropsychological treatment, 808
  - model of family adaptation, 1120
  - pediatric patient and, 308–309
  - predicting response of, 1119
  - rehabilitation process and, 826–827
  - relationships, 677
  - social isolation and, 1118
  - stress management for, 1024–1026, 1118
- Fatigue, 545–556
- anatomical mechanisms of, 525–526
  - assessment of, 525
  - basal ganglia and, 526–527
  - biochemical components of, 528
  - clinical treatment of, 528
  - definition of, 524
  - depression and, 528
  - endocrine components of, 528–529
  - epidemiology of, 524–525
  - functional mechanisms of, 527
  - management of, 530–531
  - mechanisms of, 525–527
  - neuroimaging in, 527
  - pharmacotherapy in, 985–986
  - psychology/psychiatry and, 528
  - sleep disturbances and, 529–530
  - sports-related concussion and, 411
- Feedback, in anosognosia, 782
- Feedback effects, in motor learning, 934
- Feeding, critical care nursing management and, 750–751
- Feeding ability, as factor in survival, 251
- Feinbloom charts, 519
- Feldenkrais method, 1076
- Fellowship programs, 29
- Female Sexual Distress Scale (FSDS), 683
- Female Sexual Function Index (FSFI), 683

- Ferric chloride model, of posttraumatic epileptogenesis, 450–451
- Fever, 292–293
- Fiberoptic endoscopic examination of swallow (FEES), 889–890
- Finger flexor lengthening, 643–644
- Fisher-Logemann Test of Articulation Competence, 868
- Fist deformity, 630
- Fistulas
  - carotid cavernous, 592–593
  - cerebrospinal fluid, 578–580
- FLACC Scale, 728
- Flaccid dysarthria, 867
- Flexed elbow deformity, 626–627
- Flexed hip deformity, 630–631
- Flexed knee deformity, 632–633
- Flexed wrist deformity, 628
- Flexor digitorum longus (FDL) transfer, 650–651
- Flexor lengthening, 642
- Flexor release, 642
- Flexor spasms, 618–619
- Fluid attenuated inversion recovery (FLAIR), 143, 204
- Fluid percussion injury model, of posttraumatic epilepsy, 451–452
- Fluoroscopy, swallowing disorders and, 892
- Fluoxetine, 968–969, 975, 1003
- Focal injury, 12
- Focal left hemisphere damage, 896
- Focal right hemisphere damage, 896–897
- Focal subcortical damage, 897
- Foil, Martin B., Jr., 17
- Folic acid, 1043–1044
- Foot deformity, 633–634
- Football injuries, 66–67
- Forearm, pronated, 627–628
- Forearm rehabilitation, 643
- Fractures, in older adults, 317
- Free radicals, brain injury and, 269
- Frenchay Activities Index (FAI), 226
- Frenchay Dysarthria Assessment (FDA), 868
- Frontal Assessment Battery, 852
- Frontal lobe epilepsy, 445
- Frontal regions, vulnerability of, 209–210
- Fucada Stepping Test, 540
- Fugl-Meyer index, 924
- Function, long-term decline in, 254–255
- Functional assessment, 225–246
  - activity/activity limitation methods, 238–239
  - Barthel Index, 238
  - capacity and performance, 228
  - in care of individual patients, 233–234
  - community integration questionnaire (CIQ), 239–240
  - Craig handicap assessment and reporting technique (CHART), 226, 239
  - disability rating scale (DRS), 241
  - disablement continuum, 225–227
  - functional independence measure, 226, 238–239
  - Glasgow Coma Scale, 226, 238
  - Glasgow Outcome Scale (GOS), 241–242
  - impairment/functional limitation measures, 238
  - language and, 233
  - level of cognitive function scale (LCFS), 240–241
  - Mayo-Portland Adaptability Inventory (MPAI), 241
  - measurement selection, 237–238
  - measures that cross-cut ICF domains, 240–242
  - observation in, 228–229
  - participation measure for post-acute care (PM-PAC), 240
  - participation objective, participation subjective (POPS), 240
  - participation restriction measures, 231
  - in program administration, 234–236
  - psychometric characteristics and, 229–230
  - reliability of, 230–231
  - reporting on performance of, 228–229
  - in research, 236
  - sensitivity and, 232
  - structure of assessment instruments, 227
  - subjective valuation of, 236–237
  - testing, 228–229
  - time and equipment required, 233
  - training required, 233
  - uses of, 233–236
  - validity of, 231–232
- Functional electrical stimulation (FES), 1075
- Functional Independence Measure (FIM), 35
  - disability measurement and, 277
  - in functional assessment, 226, 238–239
- Functional MRI (fMRI), 152–153, 425–427
- Functional neuroimaging, 149–156
  - disorders of consciousness and, 425–427
  - functional magnetic resonance-based imaging, 152–153
  - future research and, 153–154
  - integration with structural imaging, 220–221
  - positron emission tomography, 151–152
  - resting and activated, 149–150
  - single photon emission computed tomography, 150–151
  - sports-related concussion and, 411–412
- Functional outcome, neuroimaging correlates of. *See* Neuroimaging
- Functional plasticity, 103–105. *See also* Recovery of function
- Functional retraining, 921–924
- Functional skills training, 766



- Functional Status Examination (FSE), 35, 267–268  
Funding, for community re-entry services, 1089  
Funding issues, for older adults, 319–320
- GABA pathways  
  acute injury in, 1031  
  controversies regarding, 1032  
  recovery in, 1032
- Gabapentin, 706, 983  
Gadolinium, 133  
Gallbladder disease, 660  
Galludet, Thomas Hopkins, 15  
Gastric feeding, 665–666  
Gastritis, 658  
Gastroesophageal reflux, immobility and, 611–612  
Gastrointestinal complications, 657–661. *See also*  
  Nutrition-related complications  
  critical care nursing management and, 750  
  delayed gastric emptying, 658–659  
  diarrhea and constipation, 659–660  
  erosions, 658  
  gallbladder disease, 660  
  gastritis, 658  
  pancreatitis, 660–661  
  superior mesenteric artery syndrome, 661  
  ulcers, 658  
Gastrointestinal system, immobility effects on,  
  611–612  
Gavelston Orientation and Amnesia Test (GOAT),  
  288–289, 290, 344–346  
Gaze instability, 501–503  
  alternative strategies for, 502–503  
  exercises for vestibular adaptation, 501–502  
Gender, 113–114, 681  
Generalization, activities of daily living and, 956  
Generalized anxiety disorder (GAD), 847  
Generalized seizures, classification of, 444  
Genitourinary abnormalities, 749  
Gingko biloba, 1039–1040, 1046  
Ginseng, 1042  
Glasgow Coma Scale (GCS), 48  
  coma depth measurement, 285  
  comparing values with QEEG, 160  
  development of, 16  
  in functional assessment, 226, 238  
  in mild traumatic brain injury, 346  
  neuroimaging findings and, 145  
  in predicting outcome, 52  
  return to work issues and, 350–351  
  studies using, 177–178  
Glasgow Outcome Scale (GOS)  
  development of, 16  
  disability measurement and, 277  
  in functional assessment, 241–242  
Global assessment, nutritional, 664  
Glossopharyngeal nerve (Cranial nerve IX)  
  dysfunction, 541  
Glutamate, 84–95, 1000–1001  
Glutamine, 667  
Goal Attainment Scaling (GAS), 233  
Goal setting  
  rehabilitation process and, 826  
  strategies, 951–952  
Goldmann perimeter, 520  
Golombok-Rust Inventory of Sexual Satisfaction  
  (GRISS), 683  
Goniometry, 939  
Good-old-days bias, 389  
Gradient recalled echo (GRE) images, 206  
Gravitational shunts, 591–592  
Grief, rehabilitation process and, 828–829  
Growth hormone deficiency, 528–529, 681  
Guided imagery, 1066  
Gun safety, 68  
Gunshot wounds. *See* Penetrating injuries  
Gustatory problems, post-concussive disorder and,  
  383
- Habit reversal, for chronic pain, 737  
Habituation exercises, 499  
Haddon Matrix, 59  
Hallucinations, visual, 524  
Haloperidol, 987  
Hamilton Depression Rating Scale (HDRS), 798  
Hamstring lengthening, 647  
Hamstring release, 647–648  
Hand rehabilitation, 643–645  
Harris-Benedict (HBE) equation, 664  
Head injury  
  classification of, 271  
  morphology of, 266–268  
Head movement sensitivity, 504  
Head-shaking nystagmus, 540  
Headache Disability Rating procedure, 730  
Headaches  
  analgesic rebound headache, 716  
  cervicogenic headache, 713–714  
  chronic daily headache, 716  
  dysautonomic headache, 716  
  musculoskeletal headache, 712–713  
  neuralgic head pain, 714  
  neuritic head pain, 714  
  nutraceuticals for, 1045–1046  
  paroxysmal headaches, 716  
  post-concussive disorder and, 383  
  post-traumatic, 496, 710–712  
  post-traumatic migraine, 714–716  
  post-traumatic sinus headache, 717  
  post-traumatic tension headache, 716  
  sports-related concussion and, 410

- Healing touch therapy, 1069
- Health insurance, 5
- Health Insurance Portability and Accountability Act of 1996 (HIPAA), 1235
- Health maintenance, approach to, 59–60
- Health People 2010, 38
- Health professionals, training and certification of, 28–30
- Health related quality of life (QOL), 227
- Hearing, in older adults, 325
- Hearing loss, 381, 538–541
- Hematoma
  - epidural. *See* Epidural hematoma
  - subdural. *See* Subdural hematoma
- Hemianopsia, homonymous, 523
- Hemidystonia, posttraumatic, 475–476
- Hendler Chronic Pain Screening Test, 730
- Herniation syndromes, static neuroimaging in, 138
- Heterotopic ossification (HO), 296, 307, 645–646
- Hip adduction deformity, 646
- Hip adductor tenotomy, 646
- Hip deformity, 630–632
- Hip flexor release, 646–647
- Hip rehabilitation, 645–647
- History, in balance and dizziness problems, 497
- Hockey injuries, 67
- Holistic cognitive rehabilitation, 773–774
- Holistic habit retraining, 829
- Home-based services, 9
- Home-based therapies, 1026
- Home furnishings, in life care planning, 1227
- Homeopathy, 1063–1065
- Hopkins Verbal Learning Test (HVLT), 345
- Hormonal agents, sexual dysfunction and, 685–686
- Hormonal influences, 113–114
- Horri Oral Nasal Coupling (HONC) index, 870
- Hospital Discharge Data (HDD), 47
- Hospitalization, in older adults, 329
- Howe, Samuel Gridley, 15
- HSP 70, 85
- Human chorionic gonadotropin, 686
- Humor therapy, 1066–1067
- Hydrocephalus, 583–592
  - acute hydrocephalus, 584
  - antisiphon devices, 590
  - chronic communicating hydrocephalus, 584
  - cisternography in, 585
  - clinical presentation of, 584
  - computed tomography in, 584–585
  - CSF tap test in, 586
  - distinguishing from ex vacuo ventricular dilation, 586
  - gravitational shunts, 591–592
  - importance after TBI, 583
  - invasive testing in, 585–586
  - lumbar infusion studies and, 585
  - magnetic resonance in, 584–585
  - normal pressure hydrocephalus, 584
  - Pascal's law and, 584
  - pathophysiology of, 584
  - programmable valves, 590–591
  - pulsatile CSF flow and, 584
  - shunt complications, 588–590
  - shunt decision making, 586
  - shunt types, 587
  - shunt valves and components, 587–588
  - SPECT scans in, 585
  - static neuroimaging in, 143–144
  - sulcal absence and periventricular lucency, 585
  - treatment without shunt, 586–587
  - types and variants of, 583–584
  - ventriculomegaly and, 584–585
- Hygroma, subdural, 594
- Hyperarousal, in older adults, 325
- Hyperbaric oxygen therapy (HBOT), 1076–1078
- Hyperekplexia, 470
- Hyperglycemia, 661–662
- Hyperkinetic dysarthria, 866–867
- Hypersexual behavior, 687
- Hypersomnia, 985
- Hypertension, 290, 748
- Hypertonia, 940–941
- Hypertrophic ossification (HO), 752
- Hyperventilation, 274
- Hypoattention, in older adults, 325
- Hypochondriasis, 805
- Hypoemotionality, 1213
- Hypoglossal nerve (Cranial nerve XII) dysfunction, 542
- Hypogonadism, 681
- Hypogonadotropic hypogonadism, 681
- Hypokinetic dysarthria, 866–867
- Hypopituitarism, 680, 684
- Hyposmia, central, 532
- Hypotension, 286, 291, 745
- Hypothermia, 112
- Hypoxia, 744–745
- Iatrogenesis, post-concussive disorder and, 386–387
- Iatrogenic bias, 1186
- ICD-9-CM coding, 48
- Ictal focal neurological deficits, 447
- Illness Behavior Questionnaire (IBQ), 730
- Imagery and hypnosis, for chronic pain, 737
- Immobility, 605–614
  - antioxidant disruption and, 607
  - atrophy and, 607
  - balance disorders and, 611
  - bone density loss and, 606–607
  - cardiovascular system effects, 608–610

- cognitive and psychiatric function and, 610–611  
 complication prevention, 612  
 constipation and abnormal absorption and, 611  
 endocrine system effects, 611  
 gastroesophageal reflux and, 611–612  
 gastrointestinal system effects, 611–612  
 incoordination and, 611  
 integumentary system effects, 610  
 joint contractures and, 608  
 metabolic system effects, 611  
 muscle weakness and, 607  
 musculoskeletal impairments and, 941  
 musculoskeletal system effects, 605–608  
 neurological system effects, 610–611  
 postural hypotension and, 608–609  
 protein breakdown and, 607  
 protein synthesis and, 607  
 respiratory system effects, 608  
 thrombogenesis and, 609–610  
 urinary stasis and, 612  
 urologic system effects, 611–612
- Immune enhancing formulas, 667–668
- Impairment and disability evaluation, 1183–1204. *See also* Response bias  
 attribution and bias, 1185–1186  
 examination strategies, 1188–1197  
 examinee response biases, 1184–1185  
 major obstacles in, 1197–1198  
 models for, 1198  
 Motivational Assessment Profile-Brain Injury  
 Examinations (MAP-BI), 1193–1196  
 response bias assessment, 1187–1188  
 response bias importance, 1183–1184  
 validity enhancement recommendations, 1198–1199
- Impotence. *See* sexual dysfunction
- Impulsivity, 828, 838–839
- Incontinence, 749
- Incoordination, immobility and, 611
- Independent function aids, in life care planning, 1226
- Independent medical examinations, 1157–1158
- Individualized education programs (IEP), 9
- Individuals with Disabilities Education Act of 1990, 9
- Infection, intracranial, 581–583
- Infertility, 691
- Inflammation  
 regeneration and, 90–91  
 secondary tissue damage and, 113
- Information processing, 780–781, 784–785
- Informativeness, 901
- Informed consent, 1173, 1236
- Injury  
 characteristics in posttraumatic seizures, 453  
 molecular basis for, 268–269  
 pathophysiology for, 268–269  
 profile, neurobehavioral sequale and, 835–836  
 severity profiles in older adults, 316
- Injury control theory, 58–59
- Inpatient rehabilitation, 7
- Insomnia, 557–558. *See also* Sleep disturbances
- Insomnia questionnaires, 563–564
- Instrumental activities of daily living (IADL), 947–960
- Instrumental approach, to dysarthric speech rehabilitation, 871, 872
- Instrumental assessment, in swallowing disorders, 889–891
- Instrumental association, of dysarthria, 869
- Insulin-growth factor 1, 111
- Intact structures  
 anatomic alterations after injury, 920–921  
 neurophysiologic alterations after injury, 919–920
- Integumentary system, immobility effects on, 610
- Intellectual functioning, 782–783
- Intensive attention, 780
- Intention tremor, 470
- Intercortical microstimulation, 920
- Interdisciplinary teams, behavior disorders and, 755
- International Brain Injury Association (IBIA), 17
- International Classification of Diseases (ICD-10), 377–379
- International Classification of Functioning, Disability and Health (ICF), 34
- International Data Coma Bank, 285
- International perspectives  
 conferences, 23  
 journals, 23  
 modern era, 21–23  
 organizations, 23–24  
 support group, 24–25
- Interventions  
 cognitive-behavioral for family members, 1021–1028  
 culturally sensitive, 1027  
 home-based therapies, 1026  
 mild traumatic brain injury and, 349–350  
 for sexual behavior disorders, 687  
 for substance abuse, 1110–1113  
 timing of, 1027
- Intestinal feeding, 665–666
- Intoxication at time of injury, 1108–1109
- Intracavernosal injection, 686
- Intracerebral contusions, 272
- Intracerebral hemorrhage, 595
- Intracortical microstimulation (ICMS), 917
- Intracranial complications. *See* Late intracranial complications
- Intracranial pressure, 270, 273–275, 286, 745
- Intracranial traumatic aneurysms, 592
- Intraventricular hemorrhage, 143



- IQ tests, 783  
IRF-Patient Assessment Instrument (IRF-PAI), 235  
Irritability, 839  
Ischemia, posttraumatic, 83–84
- Jebsen Taylor Hand Function test, 939  
Jennett, Bryan, 16  
JFK Coma Recovery Scale (CRS), 429  
Job advocacy and planning, 809–810  
Job search, 1139–1141  
Joint contractures, immobility and, 608  
Joint mobility, 940–941  
Journals, international, 23  
Jugular venous oxygen saturation, 276
- Karen Ann Quinlian case, 1218  
Kava, 1042  
Kenny Self-Care Evaluation, 949  
Kessler, Howard, 16  
Kindling models, of posttraumatic epileptogenesis, 451  
Kinesiophobia Scale (K-Scale), 729  
Kinetic tremor, 470  
Klein-Bell ADL Scale, 229, 949  
Knee deformity, 632–633  
Knee extension deformity, 648  
Knee rehabilitation, 647–648  
Known group validity, of functional assessment instruments, 231  
Kohlman Evaluation of Living Skills, 949  
Krimsky Test, 518
- L-dopa/carbidopa, 979  
Labyrinthine concussion, 493–494  
Lancaster Red/Green Test, 518  
Language  
    comprehension, 998  
    development in pediatric patient, 308  
    disturbances of, 998  
    domains of, 997–998  
    functional alterations in, 853  
    neurochemistry of impairments, 998  
    skills tests, 797  
Language disorders  
    aphasia, 896–897  
    diffuse axonal damage, 897  
    focal left hemisphere damage, 896  
    focal right hemisphere damage, 896–897  
    focal subcortical damage, 897  
    site of lesion and, 895–897  
Laryngeal function, physiological measures of, 869  
Laryngotracheal mucosal reaction, 292  
Late intracranial complications, 577–602  
    basal skull fractures and, 578  
    brain abscess, 581–583  
    carotid cavernous fistulas, 592–593  
    cerebrospinal fluid fistulas, 578–580  
    cerebrospinal fluid otorrhea, 580  
    cerebrospinal fluid rhinorrhea, 578–579  
    craniectomy and, 583  
    cranioplasty and, 583  
    depressed skull fractures and, 578  
    epidural hematomas, 595  
    hydrocephalus and, 583–592  
    hygromas, 593–595  
    infectious complications, 581–583  
    intracerebral hemorrhage, 595  
    lesions, 593–595  
    meningitis, 579–580, 581  
    penetrating injuries and, 578  
    pneumocephalus, 580  
    risk of infection and, 578–580  
    subdural empyema, 581  
    subdural hematomas, 593–595  
    traumatic aneurysms, 592  
    vascular complications, 592–593  
Late posttraumatic seizures, 275  
Latent synapses, 103–105  
Learning, remediation strategies in, 810  
Legal issues. *See* Medicolegal issues  
Legislation, injury prevention programs and, 60  
Length of stay (LOS), 234  
Lesbian, gay, bisexual, transgender, and intersex (LGBTI) issues, 679  
Level of Cognitive Function Scale (LCFS), 240–241  
Levels of care, for older adults, 321  
Levirpiracetam, 1040–1041  
Life care planning, 1233–1240  
    basic ethical issues, 1236  
    case study, 1238–1240  
    clinical and forensic issues, 1233–1236  
    confidentiality and, 1236  
    elements of, 1226–1232  
    existing standards and, 1236  
    general procedures, 1232–1233  
    history of, 1223–1225  
    informed consent and, 1236  
    planning team, 1228–1232  
    professional preparation, 1236  
    RAPEL approach, 1225–1226  
Life expectancy, 247–262  
    causes of death after TBI, 248–249  
    estimation in individual cases, 256–257  
    factors related to survival, 251–253  
    female, 253  
    long-term decline in function, 254–255  
    male, 253  
    multiple factors and, 257  
    new estimates of, 253–254  
    quality of care and, 255–256

- recent literature on, 249–251
  - terminology regarding, 247–248
- Linguistic deficits, 873–879
- assessment of, 876–877
  - behavioral/restorative approaches, 877
  - case reports, 878–879
  - compensatory approaches, 877
  - pediatric considerations, 878
  - recommended assessment battery, 877
  - taxonomy and neural substrates, 873–876
  - treatment approaches, 877
- Lithium
- in affective dysregulation, 876
  - in chronic aggression, 983–984
  - in mania, 973
  - sleep disturbances and, 569
- Litigation stress, post-concussive disorder and, 390–392
- Lobular atrophy, 214
- Loneliness, as long-term problem, 279
- Long-term care. *See also* Community re-entry programs
- need for, 1085–1086
  - program design and treatment models, 1087–1088
- Longitudinal fractures, 538
- Loss of consciousness (LOC), sports-related
- concussion and, 408–409
- Low level neurological states, nursing care and, 747–754
- Lumbar infusion studies, in hydrocephalus, 585
- Lumbar puncture, 582
- Macrolinguistic analyses, 900–901
- Maddox Rod Test, 518
- Magnetic resonance imaging (MRI). *See also* Neuroimaging
- in brain contusions, 134–136
  - in cerebral edema, 139–140
  - in dystonia, 476, 478
  - in hydrocephalus, 584–585
  - imaging technique, 131–133
  - in post-traumatic fatigue, 527
  - predicting outcome and, 144–147
  - prognosis studies, 172–176
  - in shearing injuries, 136–138
  - in sports-related concussion, 411–412
  - in tremors, 473–474
- Magnetic resonance spectroscopy (MRS), 187
- Magnetoencephalography (MEG), 220
- Maladaptive behaviors, as factor in survival, 252–253
- Malingering, 390–392, 1187, 1197
- Mania, 973–974
- carbamazepine in, 973
  - lithium in, 973
  - valproate in, 973–974
  - verapamil in, 974
- Manic syndromes, 844
- Manipulative personality traits, 1186
- Mannitol, in lowering intracranial pressure, 274
- Marcus-Gunn pupil, 519
- Marital interventions, in neuropsychological treatment, 808
- Mayo-Portland Adaptability Inventory (MPAI), 241
- McGill Pain Questionnaire, 728
- Mechanical injury, to arousal system, 996
- Medial temporal lobe damage, 218–219
- Medicaid, 5, 18, 319–320
- Medicaid Buy-In provisions, 1136
- Medical complications, in older adults, 317
- Medical history, 682
- Medical malpractice cases, 1156
- Medical management, community re-entry programs and, 1098–1100
- Medical professionals
- academic subspecialty, 29–30
  - fellowship programs, 29
  - residency programs, 29
  - training and certification of, 28–30
- Medical treatment, in tremor, 480
- Medicare, 5, 18, 319
- Medication
- management for older adults, 320
  - needs in life care planning, 1227
  - review for sexual dysfunction, 683–684
  - side effects, 854
- Medicine. *See also* Cognitive impairment
- pharmacotherapy; Neuropsychiatric pharmacotherapy
- Medicolegal issues, 1151–1162. *See also* Clinico-legal examinations: Ethical issues
- capacity issues, 1152–1153
  - competence issues, 1152–1153
  - demonstrative evidence, 1159–1160
  - do not resuscitate laws, 1153–1155
  - expert witness testimony, 1158–1159
  - finding attorney, 1151–1152
  - independent medical examinations, 1157–1158
  - issue spectrum, 1151
  - lay witness testimony, 1159
  - medical malpractice cases, 1156
  - personal injury cases, 1155–1156
  - recovery protection and preservation, 1161
  - right to die laws, 1153–1155
  - workers compensation cases, 1155
- Meditation, 566, 1065–1066
- Melatonin, 563, 567–568, 1045
- Memantine, 1001
- Memory, 997
- declarative memory, 997

- Memory (*continued*)  
procedural memory, 997  
remediation strategies in, 810
- Memory deficits, 783–785  
external cueing and environmental compensations, 770–771  
external memory compensations, 770  
information processing and, 784–785  
post-traumatic amnesia, 784  
prospective memory, 770  
remediation of, 769–771
- Memory diaries, 954
- Mendelsohn maneuver, 891
- Meneire's disease, 493–494
- Meneire's syndrome, 382
- Meningitis, 581–582  
as cause of death after TBI, 249  
cerebrospinal fluid and, 579–580
- Meperidine, 707
- Message therapy, 1069–1070
- Metabolic system, immobility effects on, 611
- Metacognitive remediation, 767
- Methylphenidate, 530, 972, 979, 1006–1007, 1008–1009, 1031
- Michael Martin case, 1219
- Michigan Alcohol Screening Test (MAST), 799
- Microlinguistic analysis, 899–900
- Micronutrient supplementation, 666
- Migraine headaches, 496, 701, 714–716
- Milbank, Jeremiah, 15
- Mild traumatic brain injury, 333–372  
Alzheimer's disease risk, 359–360  
amnesia and, 342–343  
CDC Working Group criteria for, 335  
complicated, 343–344  
depression and, 351, 357–358  
early intervention, 349–350  
EFNS classification guidelines, 335  
meta-analyses results, 346–349  
National Center for Injury Prevention and Control  
definition of, 334  
neuropsychological outcome and, 342–349  
pathoanatomy of, 336  
pathophysiology of, 336–339  
persistent postconcussion syndrome and, 360  
post-traumatic confusion and, 342–343, 344–346  
post-traumatic stress disorder and, 358–359  
return to work and, 350–351, 352–356  
S-100B and, 339–342  
terminology regarding, 333–336  
U.S. Congress definition of, 334
- Millon Behavioral Health Inventory (MBHI), 730
- Millon Clinical Multiaxial Inventory, 731
- Mini-Mental Status Exam, 852
- Minimally conscious state (MCS), 254. *See also*  
Disorders of consciousness (DOC)  
definition of, 424–425  
emergence from, 425  
neuropathology of, 425  
outcomes following, 435–436
- Minimally responsive patient, 286–287
- Minnesota Multiphasic Personality Inventory (MMPI), 231, 731, 798
- Mirtazapine, 971, 1030
- Missouri Assisted Gait (MAG) scale, 943
- Mitochondrial function, 114
- Mitogen activated protein kinases (MAPK), 87
- Mobility  
driving after TBI, 1091–1097  
as factor in survival, 251  
in older adults, 327  
paratransit services, 1097–1098  
public transportation, 1097–1098
- Modafinil, 531, 1011
- Model Policy for the Use of Controlled Substances for the Treatment of Pain*, 708–709
- Modeling and interventions, 822–823
- Moderate TBI, prognosis studies, 179–180
- Modular dysfunction, 782
- Molecular basis for injury, 266–268
- Monamine oxidase inhibitors (MAOI), 971–972
- Monocular blindness, 533
- Monocular vision, 525
- Mood alterations, in older adults, 326
- Mood disorders, 842–844  
in older adults, 329  
tests affecting, 804
- Mood instability, 853
- Morbidity  
data availability, 47  
in older adults, 317  
recent epidemiological findings, 50
- Morningness-Eveningness Questionnaire (MEQ), 564
- Morphine, 706
- Morphology of head injury, 266–268
- Mortality  
data availability, 47  
in older adults, 317, 329–330  
post-traumatic seizures and, 450  
recent epidemiological findings, 50  
from severe TBI, 277
- Mothers Against Drunk Driving (MADD), 71
- Motion perception testing, 520
- Motion sensitivity, 503–504  
head movement sensitivity, 504  
visual motion sensitivity, 504–505
- Motivation, in neuropsychological assessment, 800
- Motivation disorders, 839–840

- Motivational Assessment Profile- Brain Injury Evaluations (MAP-BI), 1193–1196
- Motivational impairments, 999
- Motor Activity Log (MAL), 923, 924
- Motor and sensory functions tests, 796
- Motor control
  - motor cortex modifications, 917–918
  - motor cortex organization, 915–917
  - neural correlates of, 915–918
- Motor Control Test (MCT), 498
- Motor cortex
  - organization of, 915–917
  - plasticity in, 917
  - structural changes in, 917–918
  - topography of, 917–918
- Motor disability
  - functional retraining principles, 921–924
  - neurofacilitative approach principles, 921
  - physiotherapeutic treatment in, 921–925
- Motor evoked potentials (MEP), 925
- Motor learning principles, 933–935
  - feedback effects, 934
  - practice conditions and, 933–934
- Motor skill acquisition, 931–933
- Motor system control, 492–493
- Motor vehicle accidents, 60
- Motorcycle accidents, 61–62
- Movement disorders, 469–490
  - ballism, 476–477, 484
  - chorea, 476–477, 484
  - dystonia, 475–476, 484
  - epidemiology of, 470–471
  - frequency secondary to brain injury, 471–472
  - general pathomechanisms in, 471–472
  - Parkinson's disease, 478–480
  - paroxysmal dyskinesias, 477–478, 484
  - phenomenological classification of, 469–470
  - post-traumatic Parkinsonism, 478–480, 484
  - tics, 478
  - Tourettism, 478
  - treatment of, 480–485
  - tremors, 472–475, 480–484
- Multidetector CT (MDCT), 131
- Multidimensional Pain Inventory (MPI), 564, 728
- Multifocal electroretinograms (mfERG), 521
- Multifocal visual electrophysiology, 521
- Multimodal assessments, 35
- Multiple Sleep Latency Test (MLST), 564
- Multiple trauma, in older adults, 317
- Multisensory stimulation programs, 287
- Multisystem complications, 746
- Muramyl peptides, 563
- Muscle atrophy, 1047
- Muscle contracture, 621–624, 940–941
- Muscle overactivity, 294. *See also* Upper motoneuron syndrome
- Muscle stiffness, 621–624
- Muscle tone abnormalities, 752, 939–940
- Muscle weakness, immobility and, 607
- Musculoskeletal complications, 751–752
- Musculoskeletal headache, 712–713
- Musculoskeletal impairments, 940–941
  - joint mobility, 940–941
  - muscle contracture, 940–941
  - weakness and deconditioning, 941
- Musculoskeletal system, immobility effects on, 605–608
- Music therapy, 1067
- Myoclonus, 470
- N-methyl-D-aspartate (NMDA), 109–110
- Nancy Beth Cruzan case, 1218
- Narcolepsy, 559
- Narrative discourse
  - coherence, 900–901
  - cohesion, 900
  - impairments, 906–907
  - informativeness, 901
  - macrolinguistic analyses, 900–901
  - microlinguistic analysis, 899–900
  - story grammar, 901
  - syntax, 899–900
- Narrative discourse, lexical-semantic function, 900
- Nasometers, 870
- National Brain Injury Research, Treatment, and Training Foundation (NBIRTT), 18
- National Committee on Viral and Health Statistics (NCVHS), 235
- National Council on Disability (NCD), 16
- National Head Injury Foundation (NHIF), 16–17
- National Hospital Ambulatory Medical Care Survey (NHAMCS), 47
- National Institute on Disability and Rehabilitation Research (NIDRR), 1102
- Natural sleep aids, 567–568
- Naturopathy, 1063–1065
- Nefazodone, 971
- Negative reinforcement, 818–822
- Negative thoughts, 1028
- Nerve blocks, 638–640
- Nerve growth factor (NGF), 111
- Neural compensation, 919
- Neural networks, prognosis studies and, 188–189
- Neural recovery therapies, 109–126
  - acute cholinergic therapy, 116–117
  - blocking receptor activation and, 110
  - calcium channel blockers and, 110
  - catecholamine agonists and, 114–115

- Neural recovery therapies (*continued*)  
environmental enrichment and, 117–118  
ethanol and, 113  
excitotoxicity and, 109–110  
excitotoxin release inhibition, 109  
exogenous growth factors and, 111  
hormonal and gender influences and, 113–114  
hypothermia and, 112  
inflammation and, 113  
mitochondria and, 114  
nutraceuticals in, 118–119  
oxidative injury and, 110–111  
protease inhibitors and, 112–113  
serotonin and, 115–116  
stem cell therapy and, 118
- Neural system impairments, 938–940  
abnormal muscle tone, 939–940  
balance and vestibular disorders, 940  
voluntary and purposeful movement, 938–939
- Neuralgic head pain, 714
- Neuritic head pain, 714
- Neuro-ophthalmology, 516–517
- Neuro-optometric rehabilitation, 517–519
- Neurobehavioral functioning assessment, 797
- Neurobehavioral Functioning Inventory (NFI), 730, 798
- Neurobehavioral rating instruments, 852
- Neurobehavioral Rating Scale (NBR), 798, 852
- Neurocognitive driving test (NDT), 1095
- Neurocognitive function recovery. *See* Cognitive rehabilitation
- Neurodevelopmental treatment (NDT), 935, 939
- Neuroendocrine dysfunction, 679–681  
anterior pituitary dysfunction, 681  
clinical evaluation of, 680–681  
hypopituitarism, 680  
posterior pituitary dysfunction, 680–681  
precocious puberty, 681  
seizure disorders and, 681–682
- Neurofacilitative approaches, motor disability and, 921
- Neuroimaging  
functional. *See* Functional neuroimaging  
outcomes and, 201–224  
of acute injury, 210–211  
anterior commissure and, 218  
basal forebrain damage and, 218  
clinician based rating methods for, 214–220  
day-of-injury computerized tomography, 211–214  
diffuse brain injury and, 206–210  
frontal and temporal regions vulnerability and, 209–210  
lobular atrophy and, 214  
medial temporal lobe damage and, 218–219  
new techniques, 221  
structural and functional imaging integration, 220–221  
ventricular dilation and, 215–217  
white matter hyperintensities and, 215  
for posttraumatic fatigue, 527  
static. *See* Static neuroimaging
- Neurological complications, nursing care and, 746
- Neurological recovery, posttraumatic seizures and, 449
- Neurological systems  
immobility effects on, 610–611  
sexuality and, 675–676
- Neuromodulation, in disorders of consciousness, 430, 432–433
- Neuromonitoring technologies, 275–276
- Neuromotor assessment, 521
- Neuronal cell death, 87–88, 1025
- Neuronal reorganization, 103–105
- Neuropathic pain, 322, 717
- Neuropathology, of disorders of consciousness, 425
- Neuropharmacology  
cholinergic system and, 1026–1027  
dopamine pathways and, 1027–1028  
early *vs.* late effects, 1024–1025  
enhancing neuroplasticity, 1025  
GABA pathways and, 1031–1032  
medication principles, 1024–1025  
neuroprotective agents, 1025  
neurotransmitter systems and, 1026–1032  
norepinephrine pathways and, 1030–1031  
rehabilitation perspective, 1023–1035  
serotonergic pathways and, 1028–1030
- Neurophysiologic evaluation, for sexual dysfunction, 684
- Neurophysiology, sleep, 562
- Neuroplasticity  
definitions of, 99–100  
enhancement of, 1025
- Neuroprotectants, endogenous, 85
- Neuroprotective agents, 1028
- Neuropsychiatric aspects of TBI, 835–862  
affective instability, 839  
anxiety disorders, 847–849  
apathy, 839–840  
awareness deficit, 839  
behavioral interventions, 855–856  
cognitive syndromes, 838  
dementia, 850–851  
depression, 842–844  
dysexecutive syndromes, 838  
environmental interventions, 855–856  
impulsivity, 838–839  
injury profiles and behaviors, 836, 840–841  
irritability, 839



- manic syndromes, 844
- mood disorders, 842–844
- motivation disorders, 839–840
- neurobehavioral rating instruments, 852
- neuropsychiatric assessment, 851–853
- neurotransmitter changes, 836–837
- personality changes, 837–840
- psychiatric disorders, 841–842
- psychotic syndromes, 844–847
- social comportsment, 838–839
- substance abuse and, 849–850
- treatment principles in, 853–856
- Neuropsychiatric assessment, 851–853
  - etiology attribution, 851–853
  - formulation and interpretation, 853
  - multiple sources need and, 851
  - post-injury change assessment, 851
  - pre-injury baselines and, 851
- Neuropsychiatric Inventory, 852
- Neuropsychiatric pharmacotherapy
  - affective dysregulation and, 974–976
  - aggression and agitation and, 981–985
  - anxiety disorders and, 976–977
  - apathy and, 977–979
  - coldness and, 986
  - depression and, 967–972
  - fatigue and, 985–986
  - general principles of, 964–966
  - mania and, 973–974
  - medicine fear and, 987
  - patient evaluation and, 964
  - in persons with TBI, 964–966
  - post-traumatic stress disorder and, 976–977
  - psychosis and, 979–980
  - sleep disturbances and, 985
- Neuropsychological outcome, in mild traumatic brain injury, 342–349
- Neuropsychological assessment, 780–781, 791–814
  - behavioral observations, 794
  - checklist of behaviors, 792
  - clinical interviews, 794
  - clinical neuropsychology principles, 791–792
  - cognitive and academic functioning, 794–797
  - decision making capacity and, 1210–1211
  - differential diagnosis, 803–805
  - family and caregiver assessment, 801
  - judgment and safety, 797–799
  - motivation and effort assessment, 800
  - neurobehavioral functioning, 797
  - pain assessment, 800
  - pediatric patient and, 307–308
  - premorbid functioning comparisons, 801
  - prognosis and, 180, 801
  - qualitative assessment, 794
  - recommendations and treatment planning, 801–803
  - records review, 792–794
  - referrals and, 792
  - report writing, 806–807
  - substance abuse assessment, 799–800
  - tests and area of functioning, 796–797
  - vocational assessment, 800–801
- Neuropsychological impairment, in older adults, 328–329
- Neuropsychological treatment, 807–810
  - behavior management, 809
  - cognitive remediation, 809–810
  - education and referral, 807–808
  - family and marital intervention, 808
  - individual psychotherapy, 808
  - job advocacy and planning, 809–810
  - support groups, 808–809
- Neuropsychologist questions, in life care planning, 1230
- Neurorehabilitation, 929–946
  - behavioral treatment strategies, 937–938
  - disablement model, 929–931
  - exercise principles, 935–936
  - innovations in, 941–943
  - motor learning principles, 933–935
  - motor skill acquisition after injury, 931–933
  - musculoskeletal impairments, 940–941
  - neural system impairments, 938–940
  - physical impairment-focused interventions, 938
  - skill acquisition and available resources, 936–943
- Neurorehabilitation nursing care, 743–762
  - acute/subacute rehabilitation, 747–754
  - behavior definition and, 754–755
  - behavioral interventions and, 755
  - cardiovascular abnormalities and, 748–749
  - clinical pathways and, 746
  - critical care management, 744–747
  - environmental definitions and, 755–756
  - falls and, 756–757
  - family dynamics and, 746, 752–754
  - gastrointestinal abnormalities and, 750
  - genitourinary abnormalities and, 749–740
  - hypotension and, 745
  - hypoxia and, 744–745
  - interdisciplinary teams and, 755
  - intracranial pressure and, 745
  - low-level neurologic states and, 747
  - neurological complications and, 746
  - noxious stimuli and, 746
  - nutrition and feeding, 745, 750–751
  - pain and, 746
  - patient assessment, 754
  - pharmacological interventions and, 757–758
  - physical restraints and, 756–757
  - positioning and, 745
  - post-acute cognitive rehabilitation, 754–758

- Neurorehabilitation nursing care (*continued*)  
prehospital nursing care, 744  
primary and secondary brain injury and, 743  
rehabilitation services in ICU, 747  
respiratory abnormalities and, 748  
sensory/environmental stimulation and, 747–748  
skin care and, 752–753  
spasticity and musculoskeletal complications and, 751–752  
staffing and, 757  
suctioning and, 745  
supportive interventions and, 746–747, 753–754  
wandering and, 757
- Neurostimulant medications, 1028
- Neurotransmitter systems, 1026–1032
- Neurotrauma Foundation (NTF), 18
- Neutrality, clinical, 1170–1171
- Nitric oxide, 269
- Nocebo effect, 389
- Nocturnal sleep-related eating disorders, 560
- Nogo receptor, 920
- Non-pharmacologic pain management, 709–710
- Non-steroidal anti-inflammatory medications (NSAIDs), 322
- Noncommunicating hydrocephalus, 144
- Noncompliance, rehabilitation process and, 828
- Nonepileptic seizures (NES), 445
- Nonfatal TBI, recent epidemiological findings, 51
- Nonverbal memory tests, 796
- Norepinephrine pathways, acute injury in, 1031
- Normal pressure hydrocephalus (NPH). *See* Hydrocephalus
- Nortriptyline, 970
- Noxious stimuli, 746
- Numeric Rating Scale (NRS), 728
- Nursing care. *See also* Neurorehabilitation nursing care
- Nursing facility rehabilitation, 7–8
- Nutraceuticals, 118–119, 1037–1050  
aggression and, 1044–1045  
behavioral disturbances and, 1042–1044  
cognition improvement and, 1037–1042  
curcumin, 1046  
depression and, 1044–1045  
headache and, 1045–1046  
muscle atrophy and, 1047  
vestibular dysfunction and, 1046  
vitamin supplementation, 1046–1047
- Nutrition-related complications  
barbiturates and, 663  
cerebral salt wasting, 662  
hyperglycemia, 661–662  
seizures, 662–663  
syndrome of inappropriate secretion of antidiuretic hormone, 662
- Nutritional assessment, 664–665  
calculating protein and calorie requirements, 664–665  
subjective global assessment, 664  
weight loss expectations, 665
- Nutritional support, 293–294, 665–669  
appropriate formula choice, 666  
arginine and, 666–667  
bowel regimens and, 669  
care plan monitoring, 666  
critical care nursing management and, 745, 750–751  
dysphagia and, 668  
gastric feeding *vs.* intestinal feeding, 665–666  
glutamine and, 667  
immune enhancing formulas, 666–668  
micronutrient supplementation, 666  
in older adults, 323  
parenteral nutrition, 666  
realistic body weight maintenance, 668–669  
in rehabilitation environment, 668–669  
therapy goals of, 663–664  
withdrawal of, 669
- Nylen-Ba'ra'ny testing, 539–540
- Nystagmus, 539–540
- Objectivity, clinician, 1170
- Observation, in functional assessment, 228–229
- Obsessive-compulsive disorder (OCD), 848
- Obstructive sleep apnea (OSA), 558–559
- Occipital lobe lesions, 522–523
- Occipital neuralgia, 714
- Occupational performance  
assessment of, 950  
best practice methods for accessing, 950–951
- Occupational profiles, 949–950
- Occupational therapy, 957–958
- Oculomotor function assessment, 517–519
- Oculomotor nerve (Cranial nerve III) disorders, 534–535
- Oculomotor nerve palsies, 534
- Olanzapine, 847, 980
- Older adults, 315–332  
acute injury recovery in, 317–318  
agitation and, 325–326  
Alzheimer's disease and, 328  
apolipoprotein E4 and, 328  
behavior and cognition in, 325  
case example, 327–328  
competence and capacity in, 326  
continence and, 323–324  
decreased attention and, 325  
deep venous thrombosis risk and, 322  
dementia in, 325  
demographics of aging and, 315

- depression in, 326  
 disability in, 315  
 driving and, 327  
 etiology of injury and injury prevention, 315–316  
 falls and, 64–65  
 fractures and, 317  
 funding issues and, 319  
 health after TBI in, 318  
 hearing in, 324–325  
 hospitalization and, 329  
 hypotension and, 317  
 levels of care and, 321  
 mechanisms and pathology of injury in, 316  
 medical assessment and rehabilitation and, 306–307  
 medical complications and, 317  
 medical issues and, 320  
 medication management and, 320  
 mobility and, 327  
 mood alteration and, 326  
 mood disorders and, 329  
 morbidity and, 317  
 mortality and, 317, 329–330  
 multiple trauma and, 317  
 neuropsychological impairment and, 328–329  
 nutrition and swallowing and, 323  
 pain and, 320–322  
 prognosis studies involving, 175, 178–179  
 psychosocial outcomes and, 329  
 pulmonary embolism risk and, 322  
 recreation and vocation and, 327  
 rehabilitation assessment and, 318–320  
 rehabilitation settings and, 320–321  
 safety judgment and, 326  
 seizure risk and, 322–323  
 self-care and, 327  
 sensory health and, 324–325  
 sexuality and, 326  
 smell in, 325  
 social support networks and, 319  
 substance abuse and, 323  
 taste in, 325  
 vibratory sense in, 325  
 vision in, 324
- Olfactory hallucinations, 532  
 Olfactory nerve (Cranial nerve 1) disorders, 531–533  
 Olfactory problems, post-concussive disorder and, 383  
*Olmstead v. L.C.* (527 U.S. 581), 18  
 Omega-3 fatty acids, 1044–1045  
 Ontogeny, sleep, 561  
 Open depressed skull fractures, 273  
 Operant treatment strategies, for chronic pain, 737  
 Opiate antagonists, sexual dysfunction and, 686  
 Opiates, sleep disturbances and, 569  
 Opioid analgesics, in pain management, 705, 707, 708  
 Opioid insensitive pain, 704  
 Opportunistic personality traits, 1186  
 Optic nerve atrophy, 519  
 Optic nerve (Cranial nerve II) disorders, 533–534  
 Oral feeding, 294  
 Oral rescue medicine, 708  
 Organizations, international, 24  
 Orientation Group Monitoring System, 289, 290  
 Orthopedic equipment needs, in life care planning, 1228  
 Orthotics, in life care planning, 1226–1227  
 Oswestry Low Back Pain Disability Questionnaire, 730  
 Otorrhea, cerebrospinal fluid, 580  
 Oucher Scale, 728  
 Outcome assessment tools, 34–35  
 Outcomes, in traumatic brain injury, 276–279  
 Outpatient rehabilitation, 6  
 Overdrainage, shunts, 589  
 Overt Aggression Scale, 852  
 Oxford PTA Scale, 288–289  
 Oxidative injury, 110–111
- P300 event-related potentials, 161–162  
 P50-evoked responses, 160–161  
 Pain. *See also* Chronic pain; Pain disorders  
   assessment measures with built in response bias indicators, 732  
   assessment of, 726–735  
   behavioral-psychological model, 736–737  
   cognition and, 725  
   comprehensive personality assessment instruments, 731  
   confounding effects during neurocognitive exam, 727  
   critical care nursing management and, 746  
   desensitization model for interventions, 736  
   DSM-IV diagnoses for, 805  
   factors suggestive of exaggeration, 732  
   general health functioning and behavior measures, 730  
   general psychological measures, 731  
   management of, 735–738  
   model for conceptualizing chronic pain treatments, 736  
   in neuropsychological assessment, 800  
   neuropsychological function and, 724–726  
   in older adults, 320–321  
   overview of, 723–724  
   psychological approaches to pain, 723–752  
   response bias assessment, 732–735  
   specific measures of functioning, 728–730  
   specific pain domain instruments, 728



- Pain (*continued*)  
  TBI and pain, 724–736  
  useful behavioral treatments, 737
- Pain Affect Visual Analogue Scale (VAS), 728
- Pain Anxiety Symptoms Scale (PASS), 729
- Pain Assessment Battery (PAB), 730
- Pain Catastrophizing Scale (PCS), 729
- Pain Diaries, 728
- Pain disorders, 697–722  
  analgesic rebound headache, 716  
  ascending systems, 697–702  
  central pain syndromes, 717–718  
  cervicogenic headache, 713–714  
  cluster or paroxysmal headache, 716  
  complex regional pain syndrome, 718  
  dysautonomic headache, 716  
  general guidelines for pain pharmacology, 709  
  management strategies, 703–710  
  medical management, 703–709  
  musculoskeletal headache, 712–713  
  neuralgic head pain, 714  
  neuritic head pain, 714  
  neuroanatomy and neurobiology, 697–702  
  neuropathic pain, 717  
  non-pharmacological medical management, 709–710  
  pain assessment, 702–703  
  pharmacological management, 704–709  
  physical modalities, 709–710  
  postoperative pain management, 706  
  post-traumatic headache, 710–717  
  post-traumatic migraine, 714–716  
  post-traumatic sinus headache, 717  
  post-traumatic tension headache, 716  
  psychological assessment and, 703
- Pain Drawing, 728
- Pain Patient Profile, 728
- Pain-related potential (P250), 160–161
- Pain Stages of Change Questionnaire (PSOCQ), 729
- Pancreatitis, 660–661
- Papaverine, 686
- Papilledema, 519
- Paratransit services, 1097–1098
- Parenteral nutrition support, 665–666
- Parinaud's syndrome, 519
- Parkinsonism  
  after repeated head injury, 479–480  
  after single head injury, 478–479  
  classification of, 470  
  treatment of, 484
- Parkinson's disease, head trauma and, 480
- Parosmia, 532
- Paroxetine, 969
- Paroxysmal dyskinesias, 470  
  diagnosis of, 477–478  
  treatment of, 484
- Paroxysmal headaches, 716
- Partial-onset epilepsies, 446–447
- Partial seizures, classification of, 444
- Participant-proxy responses, 35
- Participation Measure for Post-Acute Care (PM-PAC), 240
- Participation objective, Participation Subjective (POPS) measure, 240
- Pascal's Law, 584
- Passionflower, 1043
- Passive aggressive traits, 1186
- Patching, in eliminating diplopia, 525–526
- Pathobiology, 81–96  
  apoptosis cascades, 85–87  
  axonal injuries, 88  
  cell signaling abnormalities, 87–88  
  cerebral swelling, 88–90  
  endogenous neuroprotectants, 85  
  excitotoxicity, 84–85  
  inflammation and regeneration, 90–92
- Pediatric perspective  
  cognition and pharmacology, 306  
  cognitive/education issues, 307–308  
  deep venous thrombosis/pulmonary embolus, 307  
  dysarthria in, 867–868  
  epidemiology, 305  
  family issues, 308–309  
  heterotopic ossification, 307  
  linguistic rehabilitation and, 878  
  outcomes, 305–306  
  post-traumatic seizures, 306–307  
  precocious puberty, 307  
  social/behavioral issues, 309–311
- Penetrating head injuries, 176, 252, 578
- Pentobarbital, 663
- Perceived Stress Scale (PSS), 731
- Perceptions of motion, 492
- Perceptual assessment, of motor speech function, 868
- Percutaneous endoscopic gastrostomy (PEG), 751
- Performance, in functional assessment, 228
- Peri-lesional regions, changes in after injury, 918–921
- Perilymphatic fistula, 495
- Peripheral nerve injuries, 295–296
- Peripheral vertigo, 539
- Peripheral vestibular disorders, 493–496
- Periventricular lucency, 585
- Personal activities of daily living (PADL), 947–960
- Personal injury cases, 1155–1156
- Personality Assessment Inventory (PAI), 731
- Personality changes, 387–389, 837–841
- Petadolex, 1045
- Phantom limb plasticity, 104, 106
- Pharmacological interventions, nursing staff and, 757–758
- Pharmacology of sleep, 562–563

- Pharmacotherapy  
of cognitive impairment. *See* Cognitive impairment  
pharmacotherapy  
of neuropsychiatric disturbances. *See*  
Neuropsychiatric pharmacotherapy
- Phenelzine, 970
- Phenol block, 638–640
- Phenomenological classification, of movement  
disorders, 469–470
- Phenytoin, 663, 987
- Phosphatidylcholine, 1037–1038
- Phosphodiesterase inhibitors, 684–685
- Phylogeny, sleep, 561–562
- Physical impairment-focused interventions, 938
- Physical management, in disorders of consciousness,  
431–432
- Physical modalities, in pain management, 709–710
- Physician questions, in life care planning, 1229
- Physiologic response, to brain injury, 269–271
- Physiotherapeutic treatment  
efficacy assessment and, 924  
in motor disability, 921–925  
treatment groups and valid controls, 924–925
- Physostigmine, 1012–1013
- Picamilon, 1042
- Picture Archiving and Communication System (PACS),  
131
- Piracetam, 1040–1041, 1046
- Pittsburgh Medical Center's Concussion Card,  
409–410
- Pittsburgh Sleep Quality Index, 564
- Pituitary dysfunction, 679–681
- Planning, remediation strategies in, 810
- Plasticity  
adaptive, 919  
central nervous system, 97–108. *See also* Recovery  
of function  
in motor cortex organization, 917
- Playground injuries, 73
- Pneumatic compression boots, 748
- Pneumocephalus, cerebrospinal fluid, 580
- Pneumonia, as cause of death after TBI, 249
- Polysomnography, 565
- Pontine lesions, 537
- Population research, 34
- Positioning patient, critical care nursing management  
and, 745
- Positive reinforcement, 818–822
- Positron emission tomography (PET), 151–152  
disorders of consciousness and, 425–426  
sports-related concussion and, 411
- Post-concussive disorder, 373–406  
anxiety and, 385–386  
British Columbia Postconcussion Symptom  
Inventory, 378–379, 404–405  
cervical injuries and, 380–381  
chronic pain and, 384  
comorbidities and, 380–386  
conclusions regarding, 392–396  
cranial trauma and, 381–384  
depression and, 385–386  
diagnostic criteria, 375–379  
differential diagnosis, 380–386  
DSM-IV criteria, 377–379  
estimates of, 373–374  
exaggeration and, 390–392  
iatrogenesis, 386–387  
ICD-10 criteria, 377–379  
litigation stress, 390–392  
malingered and, 390–392  
mild traumatic brain injury and, 393–395  
perception and reporting of symptoms, 387–392  
personality characteristics and disorders, 387–388  
social-psychological factors, 389–390  
somatic preoccupation and, 385–386  
symptom reporting and, 394  
whiplash-associated disorders and, 380–381
- Post trauma vision syndrome (PTVS), 514–516, 524
- Postconcussion syndrome, 360
- Posterior fossa epidural hematoma, 595
- Posterior pituitary dysfunction, 680–681
- Postictal focal neurological deficits, 447
- Postictal prolactin measurement, 445
- Post-traumatic amnesia (PTA), 178, 252, 285,  
287–289, 409, 784
- Post-traumatic confusion, in mild traumatic brain  
injury, 342–346
- Post-traumatic epilepsy, 146
- Post-traumatic fatigue (PTF). *See* Fatigue
- Post-traumatic headache. *See* Headaches; Pain  
disorders
- Post-traumatic ischemia, 83–84
- Post-traumatic migraine. *See* Migraine
- Post-traumatic perilymphatic fistula, 382
- Post-traumatic seizures and epilepsy, 443–468  
antiepileptic drug prophylaxis, 454–455  
antiepileptic drug selection, 456–457  
antiepileptic drug substitution, 457–458  
antiepileptic drug therapy duration, 458  
antiepileptic drug therapy effects, 457  
asymptomatic management of, 452–455  
classification of, 443–445  
cognitive and behavioral function, 449  
complications and consequences, 449  
consultation and referral, 450  
diagnosis, 455–456  
electroencephalography, 453–454  
high-risk patient identification, 452–453  
ictal *vs.* postictal focal neurological deficits, 447  
incidence of posttraumatic seizures, 447–448

- Post-traumatic seizures and epilepsy (*continued*)  
injury characteristics, 453  
management of, 455–459  
manifestations of, 445–447  
mortality and, 450  
natural history and, 448–450  
neurological recovery and, 449  
onset of, 448  
outcome and, 449  
patient characteristics and, 453  
pediatric patients and, 306–307  
post-traumatic epileptogenesis, 450–452  
recurrence of, 448–449  
risk factors for, 452–454  
status epilepticus, 449–450  
surgical treatment and, 458–459  
unclassified phenomena, 447
- Post-traumatic stress disorder (PTSD), 358–359, 828–829, 848–849
- Postural control assessment, 498
- Postural Evoked Responses (PER), 498
- Postural hypotension, immobility and, 608–609
- Postural instability, 505–508
- Postural stability  
exercises to improve, 506  
with remaining vestibular function, 505–506  
without vestibular function, 507–508
- Postural system control, 492–493
- Postural tremor, 470
- Practice conditions, in motor learning, 933–934
- Pragmatic rating scales, 904–905
- Praxis, 999
- Precocious puberty, 307, 681
- Predictive validity, of functional assessment instruments, 231
- Pregnancy, seizures and, 690
- Prehospital nursing care, 744
- Premature ejaculation. *See* Sexual dysfunction
- Premoline, 530
- Premorbid functioning comparison, 801
- Pressure ulcers, 752–753
- Primary injury, pathobiology of, 81–82
- Primary prevention, 57–80  
air bags, 73  
boxing injuries, 65–66  
car seats, 73  
child abuse, 72–73  
comprehensive injury prevention program development, 60  
cycling accidents, 65  
depression, 69  
drugs and alcohol, 69–72  
economics of TBI, 58  
fall prevention, 63–65  
football injuries, 66–67  
gun control, 68  
gun safety, 68  
Haddon Matrix, 59  
health maintenance approach, 59–60  
hockey injuries, 67–68  
injury control theory, 58–59  
motor vehicle accidents, 60  
motorcycle accidents, 61–62  
nature of prevention, 58  
pediatric head trauma, 72–73  
playground and recreational injuries, 73  
RBI *vs.* other disabling conditions, 58  
roadway design, 62–63  
seatbelt use, 60–62  
soccer injuries, 67  
sports and recreational injuries, 65–68  
violence and suicide, 68–69
- Prioceptive neuromuscular stimulation (PNF), 939
- Prism rehabilitation, 525–526
- Procedural memory, 997
- Professional role distinctions, 1168–1169
- Profile of Chronic Pain: Extended Battery Assessment, 729
- Profile of Chronic Pain: Screen, 729
- Profundus tendon transfer, 644–645
- Progesterone, 681
- Prognosis, 169–200, 284–286. *See also*  
Communication of prognosis  
age studies, 178–179  
apolipoprotein studies, 188  
article evaluation, 189–195  
clinical predictor studies, 174–175  
communication of prognosis, 181–186  
computed tomography studies, 176–177  
elderly studies, 178–179  
Glasgow Coma Scale studies, 177–178  
length of coma and, 177–178  
magnetic resonance imaging studies, 172–176  
magnetic resonance spectroscopy studies, 187  
methodology, 172  
moderate injury studies, 179–180  
neural network studies, 188–189  
neuroimaging studies, 173  
neuropsychological testing, 180  
penetrating injury studies, 179  
serum 100b studies, 187–188  
suggestions for further research, 189  
threshold value concept, 170–168
- Prognostication, in neuropsychological assessment, 801
- Program administration, functional assessment in, 234–235
- Program review and accreditation, 28
- Programmable valves, 590–591
- Prompted voiding, 749

- Prompting technique, learning compensatory strategies and, 953
- Pronated forearm, 627–628
- Prophylactic treatment, of seizures, 275
- Proprioceptive neuromuscular facilitation (PNF), 935
- Prosody, 998
- Prospective outcome assessments, 35
- Prospective Payment System (PPS), 235
- Prostaglandin-dependent humoral theory of sleep, 563
- Prostaglandin E1, 685
- Prosthesis, in life care planning, 1226–1227
- Prosthetics, in remediation of dysarthria, 871, 872
- Protease inhibitors, neural cell death and, 112–113
- Protein breakdown, immobility and, 607
- Protein kinases (PKA), 87–88
- Protein requirements, 664–665
- Protein synthesis, immobility and, 607
- Protriptyline, 979, 1011
- Pseudoseizures, classification of, 445
- Psychiatric disorders, 841–842
  - Diagnostic and Statistical Manual of Mental Disorders (DSM) nomenclature use, 842
  - labeling issues, 842
  - pediatric patient, 310–311
  - symptoms *vs.* disorder, 842
- Psychiatric function, bedrest effects on, 610–611
- Psychogenic seizures, classification of, 445
- Psychologic counseling, for older adults, 326
- Psychological approaches, pain. *See* Pain, psychological approaches
- Psychological decompensation, 1186
- Psychological denial, 782
- Psychological factors, post-concussive disorder and, 389–390
- Psychological variables, rehabilitation process and, 825–826
- Psychometric characteristics, of functional assessment instruments, 229–233
- Psychophysiological testing, 519–520
- Psychosexual Assessment Questionnaire, 683
- Psychosis, 979–980
  - atypical antipsychotics in, 980
  - considerations in antipsychotic agent use, 980
  - typical antipsychotics in, 979–980
- Psychosocial outcome, in older adults, 329
- Psychosocial Pain Inventory (PPI), 730
- Psychostimulants, cognitive impairments and, 1006–1009
- Psychotherapy, in neuropsychological treatment, 808
- Psychotic syndromes, 844–847
  - atypical antipsychotics, 847
  - injury profiles and, 846
  - treatment issues, 846–847
- Public transportation, 1097–1098
- Pulmonary embolism risk, in older adults, 322
- Pulsatile CSF flow, 584
- Pulsed electromagnetic field therapy (PEMF), 710
- Punch drunk syndrome, 479
- Punishment, in behavioral interventions, 818–822
- Pupillary reactivity to light, 533
- Pyritinol, 1040, 1046
- Qualifications, clinical, 1166
- Quantitative electroencephalography (QEEG), 160
- Quantity-Frequency-Variability Index (QFVI), 799
- Questionnaires, for sexual dysfunction, 683
- Quetiapine, 847
- Rabideau Kitchen Evaluation, 949
- Radiofrequency pulses (RF), 132
- Rancho Los Amigos Levels of Cognitive Function (LOCF) Scale, 10, 287, 754, 902, 937–938
- Random order practice, 934
- RAPEL method, 1225–1226
- Real-life contexts. *See* Community re-entry programs
- Reasoning and judgment tests, 797
- Rebellious personality traits, 1186
- Receptor activation, blocking, 110
- Records review, in neuropsychological assessment, 792–794
- Recovery of function
  - CNS reorganization and, 100–102
  - conceptual and theoretical issues in, 97–99
  - diaschisis and, 102–103
  - equipotentiality and, 100–102
  - functional inhibition and, 102–103
  - latent synapses and, 103–105
  - localization of function and, 99–100
  - neuronal reorganization and, 103–105
  - sparing and, 103–105
  - unmasking and, 103–105
  - vicariation and, 100–102
- Recovery theories, 919
- Recreational injuries, 73
- Recreational issues, in older adults, 327
- Red Lens Test, 518
- Referral, in neuropsychological assessment, 792–794
- Reflexology, 1069
- Regeneration, inflammation and, 90–91
- Rehabilitation
  - aggression and, 827–828
  - body weight maintenance in, 668–669
  - bowel regimens in, 669
  - catastrophic reaction and, 828–829
  - depression and, 828–829
  - dysphagia and, 668
  - early attention to psychological variables, 825–826
  - early intervention, 286
  - early pioneers in, 15

- Rehabilitation (*continued*)  
family issues, 826–827  
goal setting, 826  
grief and, 828–829  
impulsivity and, 828  
noncompliance and, 828  
post traumatic stress disorder and, 828–829  
social skills and, 829–830  
substance abuse and, 830, 1112–1113
- Rehabilitation Act of 1973, 16
- Rehabilitation assessment, in older adults, 318–320
- Rehabilitation plan, individualized, 296–297
- Rehabilitation service options, for older adults, 321
- Rehabilitation Services Administration, 4
- Rehabilitation settings, for older adults, 320
- Rehabilitation specialists, role of, 279
- Rehabilitative interventions, 7
- Reinforcement, in behavioral interventions, 818–822
- Relational conflict issues, 1167–1168
- Relaxation therapies, 566, 737, 1065–1067
- Reliability, of functional assessment instruments, 230–231
- REM sleep behavior disorder, 559–560. *See also* Sleep disturbances
- Remote regions, changes in after injury, 918–921
- Repetitive peripheral magnetic stimulation (RPMS), 1073
- Repetitive transcranial magnetic stimulation (rTMS), 1073–1074
- Report writing, neuropsychological, 806–807
- Reporting, in functional assessment, 228–229
- Reproductive issues for women, 689–691  
amenorrhea, 690  
coma and vegetative state, 690  
contraception, 690–691  
infertility, 690  
seizures and pregnancy, 690
- Research, 33–42  
alternatives to clinical trials, 37  
clinical trials, 35–37  
functional assessment in, 236  
outcome assessment tools, 34–35  
population research, 34  
priority areas, 38  
translational research, 37–38  
unique aspects of TBI, 34
- Residential rehabilitation, 6
- Residual impairments, 284
- Respiratory abnormalities, 748
- Respiratory disorders, 291–292
- Respiratory function, physiological measures of, 869–870
- Respiratory infections, as cause of death after TBI, 249
- Respiratory system, immobility effects on, 608
- Response appropriateness, 902–906
- Response bias  
assessment, 1187–1188  
attribution and bias, 1185–1186  
examination strategies and, 1188–1197  
examinee bias, 1184–1185  
importance of, 1183–1184  
major procedural limitations, 1191  
typical hallmark signs, 1190  
variables associated with, 1186
- Response bias assessment, 732–735
- Response predictability, 855–856
- Rest tremor, 470
- Resting functional neuroimaging, 149–150
- Restless leg syndrome, 559
- Restorative approach, to linguistic rehabilitation, 877, 878
- Retrograde amnesia, 410
- Return to play criteria, sports-related concussion and, 416–417
- Return to work, 1131–1148  
accommodations and, 1141–1142  
career development, 1136–1138  
career information interviews, 1138  
career interest assessments, 1137  
challenges in, 1133–1134  
consumer-focused assessment alternatives, 1138–1139  
disability issues, 1139–1140  
disability policy in United States, 1134–1136  
education and preparation, 1141  
employer negotiation strategies, 1139–1141  
experiential assessment, 1137–1138  
functional assessment and, 1138  
improving future outcome, 1145–1146  
international perspectives, 1143–1145  
job coaching and, 1142–1143  
job search, 1139–1141  
literature review, 1132–1133  
Medicaid Buy-In provisions, 1136  
mild traumatic brain injury and, 350–351, 352–356  
minimal intervention and, 1140  
residual skills assessment, 1139  
Ticket to Work and Self-Sufficiency Program, 1135–1136  
vocation rehabilitation specialists, 1138  
vocational assessment, 1138–1139  
work incentives, 1135–1136  
workplace supports, 1141–1143
- Rhinorrhea, cerebrospinal fluid, 578–579
- Right to die laws, 1153–1155
- Rinne Test, 540–541
- Risk factors, in posttraumatic seizures and epilepsy, 452–454
- Risperidone, 847, 980
- Roadway design, injury prevention and, 62–63



- Robert Wendland case, 1219  
Rotary stair testing, 498  
Routine fondness, 855  
Rush, Howard, 16
- S-adenosylmethionine, 1043–1044  
β-Adrenergic receptor antagonists, 984–985  
S-100B, as marker of injury, 339–342  
Safety, in neuropsychological assessment, 797–799  
Safety judgment, in older adults, 326  
Scale to Assess Unawareness of Mental Disorders, 852  
Scientific literature in TBI, 17  
Screening tests, for sexual dysfunction, 684  
Seatbelt use, 60–61  
Second impact syndrome, 415  
Secondarily generalized seizures (SGS), 444  
Secondary injury, evolution of, 82–83  
Sector prism systems, 523  
Sedation, 274  
Sedative/hypnotics, sleep disturbances and, 568–569  
Seizure disorders, neuroendocrine dysfunction and, 681–682  
Seizures. *See also* Posttraumatic seizures and epilepsy  
  antidepressants and, 972  
  pregnancy and, 690  
  providing nutrition and, 662–663  
  risk in older adults, 322–323  
  secondary insult and, 275  
  shunts and, 589  
Selective attention, 780  
Selective serotonin reuptake inhibitors (SSRI), 683, 967–968  
Self-care, in older adults, 327  
Sensitivity, of functional assessment instruments, 232  
Sensory health, in older adults, 324–325  
Sensory hearing loss, 538  
Sensory input, enhancing, 891  
Sensory Modality Assessment Rehabilitation Technique (SMART), 429  
Sensory Organization Test (SOT), 498  
Sensory pathways, 530  
Sensory stimulation, in disorders of consciousness, 430–431  
Serial seizures, classification of, 444  
Serotonergic pathways  
  acute injury in, 1029  
  controversy regarding, 1030  
  recovery in, 1029–1030  
Serotonergic system changes, 837  
Serotonin, 115–116, 1002–1003  
Serotonin reuptake inhibitors, 975, 976  
Sertraline, 967–968, 1002–1003  
Serum 100b, 187–188  
Severity and outcome, recent epidemiological findings, 51  
Severity indicators, in predicting outcome, 52  
Sex, as factor in survival, 251  
Sex therapy, 687–688  
Sexual abuse, 687  
Sexual dysfunction. *See also* Neuroendocrine dysfunction  
  after brain injury, 676–678  
  antidepressants and, 686  
  behavioral disorder interventions, 687  
  comprehensive evaluation for, 682–684  
  definitions of, 674–675  
  dopaminergic agents and, 685  
  family relationships and, 677  
  hormonal agents and, 685–686  
  intellectual impairment and, 677  
  intracavernosal injection and, 686  
  marital adjustments and, 677  
  medical history and, 682  
  medication review and, 683–684  
  natural compounds and, 686  
  opiate antagonists and, 686  
  pharmacology and, 684–687  
  phosphodiesterase inhibitors and, 684–685  
  professional and patient education, 688–689  
  prostaglandin E1 and, 685  
  prosthetic surgery and, 687  
  psychiatric dysfunction and, 677  
  psychological evaluation and, 682–683  
  questionnaires regarding, 683  
  reproductive issues for women, 689–691  
  sex therapy, 687–688  
  sexual response cycle, 678  
  in women, 687  
Sexual Function Questionnaire (SFQ), 683  
Sexual Interest and Satisfaction Scale (SIS), 683  
Sexuality  
  brainstem and related structures and, 675–676  
  chemical messengers and, 675  
  cortical systems and, 676  
  disability and, 678–679  
  issues in older adults, 326  
  neurological systems and, 675–676  
  sexual orientation issues, 679  
  sexual prejudice, 679  
  spinal systems and, 675  
  subcortical systems and, 676  
SF-36 Health Survey, 730  
Shearing injuries, 136–138  
Short-form 36 (SF-36), 227  
Short-latency SEP (SSEP), 157  
Shoulder, adducted, internally rotated, flexion restricted, 625–626  
Shoulder contracture, 641  
Shoulder lengthenings, 641–642  
Shoulder rehabilitation, 641–642

- Shunts. *See also* Hydrocephalus  
  antisiphon devices, 590  
  chronic subdural hematoma and, 589–590  
  complications using, 588–590  
  gravitational shunts, 591–592  
  infection and, 582, 588–589  
  overdrainage, 589  
  programmable valves, 590–591  
  seizures and, 589  
  shunt failure, 588  
  types of, 587  
  valves and components, 587–588
- Sickness Impact Profile (SIP), 730
- Simple partial seizure (SPS), 444
- Single photon emission computed tomography (SPECT), 146, 150–151, 220, 411
- Sinking skin flap syndrome, 583
- Sinus headaches, 717
- Skepticism, patient, 1186
- Skilled nursing facility rehabilitation, 7–8
- Skin care, critical care nursing management and, 752–753
- Skull fractures, 266, 381, 578
- Slate-Trait Anger Expression Inventory, 731
- Sleep Disorders Questionnaire, 564
- Sleep disturbances, 557–576  
  alternative/complementary medicine techniques, 566–568  
  antidepressants and, 568  
  antiepileptics and, 568  
  antihistamines and, 568  
  antipsychotics and, 569  
  assessment of, 563–565  
  behavioral and cognitive therapies, 566  
  biochemical pharmacology of wakefulness, 562  
  biofeedback and, 566  
  bright light therapy, 565  
  bruxism, 560  
  chronotherapy, 565  
  classification of, 558  
  cranial electrotherapy stimulation, 565–566  
  definitions of insomnia, 557–558  
  environmental measures, 565–566  
  epidemiology, 557  
  fatigue and, 529–530  
  insomnia questionnaires, 563–564  
  list of dyssomnias, 558  
  lithium and, 569  
  meditation and, 566  
  melatonin and, 567–568  
  narcolepsy, 559  
  nocturnal sleep-related eating disorders, 560  
  non-REM sleep, 561  
  nonpharmacologic measures, 565–568  
  objective sleep testing measures, 564  
  obstructive sleep apnea, 558–559  
  ontogeny of sleep, 561  
  opiates and, 569  
  parasomnias, 559–560  
  pharmacologic treatment, 568–569  
  pharmacology of sleep, 562–563  
  pharmacotherapy in, 985  
  phylogeny of sleep, 561–562  
  polysomnography, 565  
  related to TBI, 566  
  relaxation therapy, 566  
  REM sleep behavior disorder, 559–560  
  restless leg syndrome, 559  
  sedative/hypnotics and, 568–569  
  sleep neurophysiology, 562  
  sleep restriction, 565  
  sleep terrors, 559  
  sleep walking, 559  
  stages of sleep, 561  
  stimulus control instructions, 565
- Sleep restriction, 565
- Sleep terrors, 559
- Sleep walking, 559
- Sloan Acuity Charts, 519
- Smell  
  impaired, 531–533  
  in older adults, 325
- Soccer injuries, 67
- Social cognition, 787–788
- Social comportment, 838–839
- Social contact, decreased, 279
- Social information processing, 905
- Social isolation, 1091, 1118, 1140
- Social skills  
  pediatric patient, 309–310  
  rehabilitation process and, 829–830
- Social support networks, for older adults, 319
- Sociopathic personality traits, 1186
- Sodium amobarbital (Amytal), 706
- Soldiers Rehabilitation Act of 1918, 15
- Somatic motor pathway, 530
- Somatic preoccupation, post-concussive disorder and, 385–386
- Somatization disorder, 805
- Somatoform disorders, 1186
- Somatosensory evoked potentials (SEP), 157–158
- Sparing, 103–105
- Spastic deformities, 941
- Spastic dysarthria, 866
- Spastic dystonia, 649–620
- Spasticity, 294, 616–617, 751
- Spatial attention, 996
- Spatial cognition, 785–786
- Special education, 8–9

- Specialized transportation, 1097–1098  
Speech, alterations in, 853  
Speech and language disorders, 865–886. *See also*  
    Dysarthria; Linguistic deficits  
Spielberger State Trait Anxiety Inventory, 852  
Spinal accessory nerve (Cranial nerve XI) dysfunction,  
    542  
Spiritual healing, 1071–1072  
Spivak, Marilyn, 16  
Spivak, Martin, 16  
Split anterior tibialis tendon transfer (SPLATT),  
    649–650  
Sports injuries, 65–68  
Sports-related concussion, 407–422  
    amnesia and, 409–410  
    asymptomatic status at rest, 416  
    asymptomatic status with physical exertion, 417  
    concussion cards, 409–410  
    concussion grading scales, 415–416  
    confusion and, 409  
    cumulative effects, 413–415  
    definition of concussion, 407–408  
    injury severity markers, 408–388  
    intact neurocognitive function, 417  
    loss of consciousness and, 408–409  
    neuropsychological outcome and, 412–413  
    pathophysiology of, 408  
    recovery time, 415–417  
    return-to-play decision making, 415–417  
    second impact syndrome, 415  
    sideline or on-field testing, 409–410  
    structural and functional neuroimaging and,  
        411–412  
    symptoms, 410–411  
SPS-B, 563  
St. John's Wort, 1045  
Static neuroimaging, 129–148  
    brain contusions, 134–136  
    brain imaging, 133–144  
    cerebral edema, 138–139  
    epidural collections, 141–142  
    herniation syndromes, 138  
    hydrocephalus, 143–144  
    imaging technique, 129–133  
        computed tomography, 130–131  
        magnetic resonance imaging, 131–133  
    integration with functional imaging, 220–221  
    intraventricular hemorrhages, 143  
    predicting outcome and, 144–147  
    shearing injuries, 136–138  
    subarachnoid hemorrhages, 142–143  
    subdural collections, 140–141  
Statistical parametric mapping (SPM), 209  
Status epilepticus, 444, 449–450  
Stem cell therapy, 118  
Step training on treadmill, 942–943  
Stereotactic surgery, 480–484  
Stereotype threat, post-concussive disorder and,  
    389–390  
Stereotypy, 470  
Stiff knee deformity, 632  
Stimulants, in chronic aggression, 984  
Stimulus boundedness, 855  
Stimulus control, sleep disturbances and, 565  
Story grammar, 901  
Strength maintenance, in life care planning, 1227  
Stress  
    family, 1024–1026, 1118  
    post-concussive disorder and, 385–386  
Structural neuroimaging, sports-related concussion  
    and, 411–412  
Subacute nursing facility rehabilitation, 7  
Subarachnoid hemorrhage, 267  
Subarachnoid hemorrhage, static neuroimaging in,  
    142–143  
subconcussive blows. *See* Sports-related concussion  
Subcortical systems, sexuality and, 676  
Subdural collections, static neuroimaging in, 140–141  
Subdural empyema, 581, 582  
Subdural hematoma, 589–590, 593–595  
    differences with acute hematoma, 593  
    management of, 594–595  
    pathology of, 594  
    pathophysiology of, 595  
    scan findings in, 593–594  
    surgery for, 595  
Subdural hemorrhages, 267  
Subdural hygroma, 594  
Subjective valuation, of functional performance,  
    236–237  
Substance abuse, 69–72, 1105–1116  
    addiction concerns, 709  
    brain structure and function effects, 1107–1108  
    dementia and, 850–851  
    interventions and, 1110–1113  
    intoxication at time of injury, 1108–1109  
    in neuropsychological assessment, 799–800  
    in older adults, 323  
    prior history and, 1109  
    psychosocial consequences and, 1105–1107  
    rehabilitation process and, 830  
    risks of after TBI, 1105–1108  
    treatment of, 849–850  
    use after TBI, 1109–1110  
Substance Abuse Subtle Screening Inventory (SASSI),  
    799  
Sudden unexpected death in epilepsy (SUDEP), 450  
Suicide, 68, 69, 248–249  
Sulcal absence, 585  
Super supraglottic swallow, 891



- Superior mesenteric artery syndrome, 661
- Support groups  
  international, 24–25  
  in neuropsychological treatment, 808–809
- Supportive interventions, critical care nursing management and, 746–747, 753–754
- Supraglottic swallow, 891
- Supraspinatus slide, 642
- Surgical treatment  
  in head injury, 272–273  
  in ocular paresis, 519  
  in post-traumatic seizures, 458–459  
  in remediation of dysarthria, 871, 872  
  in tremor, 480–483
- Surrogate decision making, 1214–1217, 1218–1220
- Survey of Pain Attitudes (SOPA), 729
- Swallow measures, 891–892
- Swallowing problems, 293–294, 887–894  
  in brain injury, 887–888  
  dysphagia, 888–893  
  evaluation of, 888–889  
  family counseling and, 888  
  follow-ups, 893  
  instrumental assessments, 889–891  
  in older adults, 323  
  research needs, 893–894
- Symptom exaggeration, 1186
- Symptom magnification, 1187
- Symptom minimization, 1187
- Synaptic plasticity, 452
- Syndrome of inappropriate secretion of antidiuretic hormone (SIADH), 662, 679, 680
- Syndrome of the trephined, 583
- Syntax, 899–900
- Synthetic narcotics, 707
- Systematic functional linguistics, 903–904
- Task-specific training, 935
- Taste, in older adults, 325
- Teasdale, Graham, 16
- Teenage drinking, 69–70
- Temporal bone fractures, 494, 580
- Temporal bone lesions, 522
- Temporal regions, vulnerability of, 209–210
- Tension headaches, 716
- Tension pneumocephalus, 580
- Terri Schiavo case, 1154, 1220
- Tertiary prevention, 284–296  
  contractures, 295  
  fractures, 295  
  heterotopic ossification, 296  
  peripheral nerve injuries, 295–296  
  venous thromboembolism, 294–295
- Testing, in functional assessment, 228–229
- Testosterone delivery systems, 686
- Tetracyclic antidepressants (TCA), 970–971, 975
- Thalamic deep brain stimulation (DBS), 481
- Thenar muscle slide, 645
- Theoretical issues, recovery of function and, 97–99
- Therapeutic modalities, in life care planning, 1226
- Threshold value concept, 170–176
- Thrombogenesis, immobility and, 609–610
- Thumb-in-palm deformity, 630, 645
- Thumb rehabilitation, 645
- Tibialis posterior lengthening, 650
- Ticket to Work and Self-Sufficiency Program, 1135–1136
- Tics  
  classification of, 470  
  diagnosis of, 478
- Time since injury, as factor in survival, 251
- Tinnitus, post-concussive disorder and, 382–383
- Tizanidine (Zanaflex), 635–636, 706
- Todd's phenomena, 447
- Token economies, 821
- Topic management, 903
- Topiramate, 988
- Total quality management (TQM), 235
- Tourette's syndrome, 478
- Tracheal intubation, prolonged, 292
- Tracheotomy, 292
- Traditional Chinese medicine (TCM), 1051–1060  
  acupuncture points, 1058  
  acute severe TBI and, 1052–1053  
  chronic post brain injury syndrome, 1056–1058  
  kidney insufficiency, 1055  
  liver dysfunction, 1055–1056  
  *qi* deficiency, 1055  
  *qi* disturbance, 1052–1053  
  stagnancy of blood, 1055  
  stasis of blood, 1054–1055  
  subacute TBI and, 1053–1056
- Training and certification, 27–32  
  community careers, 30–32  
  community re-entry programs and, 1101–1102  
  medical and health professional care providers, 28–30  
  paraprofessionals, 30–32  
  program review and accreditation, 28  
  training intensity, 935–936
- Transcendental meditation, 1066
- Transcranial magnetic stimulation (TMS), 1072–1074
- Transcutaneous electrical nerve stimulation (TENS), 709–710, 1075
- Translational research, 37–38
- Transportation, patient, 5, 1227. *See also* Driving; Public transportation
- Transverse fractures, 538
- Traumatic axonal injury (TAI), 88, 338

- Traumatic brain injury  
 characteristics of, 3–4  
 marketplace realities, 5  
 problem scope, 3–4  
 systems of care development, 4–5
- Traumatic Brain Injury Act, 18
- Trazodone, 971, 985, 1030
- Treatment interventions, in disorders of consciousness, 430–433
- Treatment planning, in neuropsychological assessment, 801
- Treatment strategies, in disorders of consciousness, 436–437
- Tremor  
 after moderate and mild brain injury, 484  
 after severe brain injury, 480–484  
 classification of, 470  
 diagnosis of, 472–475  
 medical treatment, 480  
 surgical treatment, 480–483
- Tricyclic antidepressants (TCA), 970–971, 975
- Trigeminal nerve (Cranial nerve V) disorders, 535–536
- Trochlear nerve (Cranial nerve IV) disorders, 535
- Tryptophan, 1044
- Tufts assessment of motor performance (TAMP), 233
- Ulcers  
 gastric, 658  
 pressure, 752–753
- Ulnar nerve compression, 643
- Unconsciousness duration, as factor in survival, 252
- Unemployment, post-injury, 1105–1106
- Uniform Data System (UDS), 234
- Unilateral peripheral vestibular hypofunction (UVH), 501
- University of Pennsylvania Smell Identification Test (UPSIT), 532, 786
- Unmasking, 103–105
- Upper motoneuron syndrome (UMNS), 615–653  
 adducted, internally rotated, flexion restricted shoulder, 625–626  
 adducted hip deformity, 631–632  
 associated reactions and, 620–621  
 botulinum neurotoxin in, 636–640  
 clenched fist deformity, 628–630  
 clinical commentary on treatment, 625  
 clinical evaluation aspects, 624  
 co-contraction and, 618  
 conus and, 617–618  
 elbow rehabilitation, 642–643  
 equinovarus foot deformity, 633–634  
 flexed elbow deformity, 626–627  
 flexed hip deformity, 630–631  
 flexed knee deformity, 632–633  
 flexed wrist deformity, 628  
 flexor and extensor spasms and, 618–619  
 foot and ankle rehabilitation, 648–651  
 forearm rehabilitation, 645  
 hand rehabilitation, 643–645  
 hip rehabilitation, 645–647  
 knee extension deformity, 648  
 knee rehabilitation, 647–648  
 motor recover time course and, 624  
 muscle stiffness and contracture and, 621–624  
 neuro-orthopedic principles and perspective, 640  
 neuro-orthopedic treatment, 640–641  
 pharmacologic intervention, 634–640  
 pronated forearm, 627–628  
 shoulder rehabilitation, 641–642  
 spastic dystonia, 619–620  
 spasticity and, 616–617  
 stiff knee deformity, 632  
 technology evaluation aspects, 624  
 thumb-in-palm deformity, 630  
 thumb rehabilitation, 645  
 wrist rehabilitation, 643
- Uridine, 563
- Urinary incontinence, 293
- Urinary stasis, immobility and, 612
- Urinary tract infections, 292
- Urologic system, immobility effects on, 611–612
- Vagus nerve (Cranial nerve X) dysfunction, 541–542
- Vagus nerve stimulation (VNS), 459
- Valerian, 1043
- Validity, of functional assessment instruments, 231
- Valproate, 973–974, 988
- Vanderbilt Pain Management Inventory, 730
- Variability in presentation, 853
- Vascular complications, 592–593  
 carotid cavernous fistula, 592–593  
 traumatic aneurysm, 592
- Vascular evaluation, for sexual dysfunction, 684
- Vasopressin, 679
- Vegetative state (VS). *See also* Disorders of consciousness (DOC)  
 cases, 1153  
 definition of, 424  
 neuropathology of, 425  
 outcomes following, 434–435  
 pregnancy and, 690
- Velopharyngeal function, physiological measures of, 870
- Venlafaxine, 971
- Venous thromboembolism, 294–295
- Ventilator support, as factor in survival, 251
- Ventricle-to-brain ratio (VBR), 207
- Ventricular dilation, 215–217, 586
- Ventriculomegaly, 585–585
- Ventriculostomy, 273

- Verapamil, 974  
Verbal Analogue Scale, 702  
Verbal memory tests, 796  
Verbal Rating Scale (VRS), 728  
Vertical diplopia, 535  
Vertical nystagmus, 539  
Vertigo, 382, 539. *See also* Balance and dizziness  
Vestibular adaptation, 501–502  
Vestibular and balance rehabilitation therapy (VBRT), 498–508  
    appropriate candidates for, 500  
    for benign paroxysmal positioning vertigo, 500–501  
    exercise guidelines for TBI, 508  
    for gaze instability, 501–503  
    habituation exercises, 499  
    for motion sensitivity, 503–505  
    outcomes of, 508  
    for postural instability, 505–508  
Vestibular compensation process, 493  
Vestibular disorders, 493–496, 539, 940, 1046  
Vestibular lesions, 539  
Vestibulocochlear nerve (Cranial nerve VIII) disorders, 538–541  
Vestibuloocular reflex, 502  
Vestibuloocular reflex (VOR), 492, 540  
Vestibulospinal reflexes (VSR), 505  
Vibratory sense, in older adults, 325  
Vicariation, 100–102, 919, 920  
Victoria Symptom Validity Test (VSVT), 1197  
Video-electroencephalography (VEEG), 445, 455–456  
Vinpocetine, 1041–1042  
Violence, 68–69  
Visceral motor pathway, 531–531  
Vision  
    blurring of, 533  
    in older adults, 324  
    post-concussive disorder and, 383  
    rehabilitation, 525–526  
    sports-related concussion and, 411  
    therapy. *See* Visual dysfunction  
Visual acuity testing, 519–520, 533–534  
Visual Analogue Pain Scale (VAS), 702, 728  
Visual-based skills tests, 796–797  
Visual dysfunction, 511–528  
    bimodal process of vision, 512–514  
    binocular function assessment, 517–519  
    binocular intervention, 524–525  
    diplopia, 525  
    electrophysiological testing, 520–522  
    motion perception, 520  
    multifocal electroretinograms, 521  
    multifocal visual electrophysiology, 521  
    Neuro-ophthalmology, 516–517  
    neuro-optometric rehabilitation, 517–519  
    neuromotor assessment, 521  
    oculomotor function assessment, 517–519  
    post trauma vision syndrome, 514–516  
    prism rehabilitation, 525–526  
    psychophysiological testing, 519–520  
    vision rehabilitation, 523–524  
    vision therapy, 525  
    visual acuity, 519–520  
    visual evoked response, 520  
    visual field dysfunction, 522–524  
    visual field testing, 519–520  
    visual midline shift syndrome, 516  
    visual phenomena associated with TBI, 524  
    visual-vestibular integration dysfunction, 521–522  
Visual evoked response (VEP), 520  
Visual field defects, 533  
Visual field dysfunction, 522–524  
Visual field testing, 519–520, 534  
Visual midline shift syndrome (VMSS), 516  
Visual motion sensitivity, 504–505  
Visual-vestibular integration dysfunction, 521–522  
Visuospatial neglect, 523  
Vitamin B<sub>1</sub>, 1046  
Vitamin B<sub>6</sub>, 1046  
Vitamin B<sub>12</sub>, 1043–1044, 1046  
Vitamin C, 1046  
Vitamin supplementation, 1046–1047  
Vocational assessment, 800–801, 1138–1139  
Vocational issues, in older adults, 327  
Vocational plan, in life care planning, 1228  
Vocational Rehabilitation Amendments of 1954, 16  
Vocational services, 6  
Voluntary movement, impairments in, 938–939  
Voxel-based lesion-symptom mapping (VLSM), 203  
Vulnerability, heightened, 854  
  
Wakefulness, biochemical pharmacology of, 562  
Walking with Sudden Turns Test, 540  
Wandering, 757  
Weber Test, 541  
Wechsler Adult Intelligence Scale, 782–783  
Weight loss, 665  
Wernicke's hemianopic pupil, 519  
Wessex Head Injury Matrix, 429  
Western Neuro Sensory Stimulation Profile (WNSSP), 429  
Westmead PTA Scale, 289  
Wheelchair needs, in life care planning, 1226  
Whiplash-associated disorders, 380–381  
White matter hyperintensities (WHM), 215–216  
Wilbur, Harvey, 15  
Wind-up sensitization, 699  
Wisconsin Card Sorting Test (WCST), 345, 907  
Withdrawal of feedings, 669  
Wolf Motor Function Test (WMFT), 923, 924

- Women, reproductive issues for, 689–691  
Work. *See also* Return to work  
Work incentives, 1135–1136  
Workers compensation cases, 1155  
Workplace supports, 1141–1143  
    accommodations, 1141–1142  
    job coaching, 1142–1143  
Worth Four Dot Test, 518  
Wrist deformity, 628  
Wrist flexor lengthening, 643  
Wrist flexor release, 643  
Wrist fusion, 643  
Wrist rehabilitation, 643  
Yoked prism system, 523  
Ziconotide (Prialt), 706  
Ziprasidone, 847  
Zitnay, George A., 17, 18  
Zung Self-rating Depression Scale (SDS), 731