# Peripheral Neuropathy

A Medical Dictionary, Bibliography,
and Annotated Research Guide to
Internet References

**James N. Parker, M.D.**
**and Philip M. Parker, Ph.D., Editors**

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# Acknowledgements

The collective knowledge generated from academic and applied research summarized in various references has been critical in the creation of this book which is best viewed as a comprehensive compilation and collection of information prepared by various official agencies which produce publications on peripheral neuropathy. Books in this series draw from various agencies and institutions associated with the United States Department of Health and Human Services, and in particular, the Office of the Secretary of Health and Human Services (OS), the Administration for Children and Families (ACF), the Administration on Aging (AOA), the Agency for Healthcare Research and Quality (AHRQ), the Agency for Toxic Substances and Disease Registry (ATSDR), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Healthcare Financing Administration (HCFA), the Health Resources and Services Administration (HRSA), the Indian Health Service (IHS), the institutions of the National Institutes of Health (NIH), the Program Support Center (PSC), and the Substance Abuse and Mental Health Services Administration (SAMHSA). In addition to these sources, information gathered from the National Library of Medicine, the United States Patent Office, the European Union, and their related organizations has been invaluable in the creation of this book. Some of the work represented was financially supported by the Research and Development Committee at INSEAD. This support is gratefully acknowledged. Finally, special thanks are owed to Tiffany Freeman for her excellent editorial support.

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# Table of Contents

# FORWARD

In March 2001, the National Institutes of Health issued the following warning: "The number of Web sites offering health-related resources grows every day. Many sites provide valuable information, while others may have information that is unreliable or misleading."[1] Furthermore, because of the rapid increase in Internet-based information, many hours can be wasted searching, selecting, and printing. Since only the smallest fraction of information dealing with peripheral neuropathy is indexed in search engines, such as **www.google.com** or others, a non-systematic approach to Internet research can be not only time consuming, but also incomplete. This book was created for medical professionals, students, and members of the general public who want to know as much as possible about peripheral neuropathy, using the most advanced research tools available and spending the least amount of time doing so.

In addition to offering a structured and comprehensive bibliography, the pages that follow will tell you where and how to find reliable information covering virtually all topics related to peripheral neuropathy, from the essentials to the most advanced areas of research. Public, academic, government, and peer-reviewed research studies are emphasized. Various abstracts are reproduced to give you some of the latest official information available to date on peripheral neuropathy. Abundant guidance is given on how to obtain free-of-charge primary research results via the Internet. **While this book focuses on the field of medicine, when some sources provide access to non-medical information relating to peripheral neuropathy, these are noted in the text.**

E-book and electronic versions of this book are fully interactive with each of the Internet sites mentioned (clicking on a hyperlink automatically opens your browser to the site indicated). If you are using the hard copy version of this book, you can access a cited Web site by typing the provided Web address directly into your Internet browser. You may find it useful to refer to synonyms or related terms when accessing these Internet databases. **NOTE:** At the time of publication, the Web addresses were functional. However, some links may fail due to URL address changes, which is a common occurrence on the Internet.

For readers unfamiliar with the Internet, detailed instructions are offered on how to access electronic resources. For readers unfamiliar with medical terminology, a comprehensive glossary is provided. For readers without access to Internet resources, a directory of medical libraries, that have or can locate references cited here, is given. We hope these resources will prove useful to the widest possible audience seeking information on peripheral neuropathy.

*The Editors*

[1] From the NIH, National Cancer Institute (NCI): **http://www.cancer.gov/cancerinfo/ten-things-to-know**.

# CHAPTER 1. STUDIES ON PERIPHERAL NEUROPATHY

## Overview

In this chapter, we will show you how to locate peer-reviewed references and studies on peripheral neuropathy.

## The Combined Health Information Database

The Combined Health Information Database summarizes studies across numerous federal agencies. To limit your investigation to research studies and peripheral neuropathy, you will need to use the advanced search options. First, go to **http://chid.nih.gov/index.html**. From there, select the "Detailed Search" option (or go directly to that page with the following hyperlink: **http://chid.nih.gov/detail/detail.html**). The trick in extracting studies is found in the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Journal Article." At the top of the search form, select the number of records you would like to see (we recommend 100) and check the box to display "whole records." We recommend that you type "peripheral neuropathy" (or synonyms) into the "For these words:" box. Consider using the option "anywhere in record" to make your search as broad as possible. If you want to limit the search to only a particular field, such as the title of the journal, then select this option in the "Search in these fields" drop box. The following is what you can expect from this type of search:

- **Capsaicin for Diabetic Peripheral Neuropathy**

  Source: Practical Diabetology. 9(4): 4-5. July-August 1990.

  Summary: A new product, Axsain (capsaicin), is being actively promoted in various diabetes publications for the treatment of painful neuralgias (peripheral neuropathy). This article reviews the pharmacology, comparative efficacy, adverse reactions, and recommended uses for this product, which is available without a prescription. The authors are concerned about the product because of the lack of completed controlled clinical trials to examine the efficacy and safety of capsaicin in the treatment of diabetic peripheral neuropathy.

- **Walking Strategy in Diabetic Patients with Peripheral Neuropathy**

  Source: Diabetes Care. 25(8): 1451-1457. August 2002.

  Contact: Available from American Diabetes Association. 1701 North Beauregard Street, Alexandria, VA 22311. (800) 232-3472. Website: www.diabetes.org.

  Summary: Patients with diabetic neuropathy (nerve disease related to diabetes) show a peculiar loading pattern of the foot, which led the authors of this study to hypothesize that a substantial modification exists in their deambulatory strategy. This study quantifies the changes of the loading patterns and monitors the excursion of center of pressure (COP) during gait. A total of 21 healthy volunteers (C ) and 61 patients with diabetes were evaluated: 27 subjects with diabetes without neuropathy (D), 19 with neuropathy (DN), and 15 with previous neuropathic ulcer (DPU). A piezo-dynamometric platform was used to record the foot-to-floor interaction by measuring loading time and the instantaneous COP position during the stance phase of gait. Loading time was significantly longer in neuropathic patients than in control subjects. COP excursion along the mediolateral axis of the foot clearly decreased from C to DPU groups. The authors conclude that the accurate quantification of loading patterns and of COP excursions and integrals highlights changes of foot-to-floor interaction in patients with diabetic neuropathy. The corresponding changes of loading times and patterns support the authors' hypothesis that a change in the walking strategy of patients with peripheral neuropathy does occur. 6 figures. 1 table. 26 references.

- **Simple Screening Tests for Peripheral Neuropathy in the Diabetes Clinic**

  Source: Diabetes Care. 24(2): 250-256. February 2001.

  Contact: Available from American Diabetes Association. 1701 North Beauregard Street, Alexandria, VA 22311. (800) 232-3472. Website: www.diabetes.org.

  Summary: This article describes a study that assessed the operating characteristics of four simple sensory screening maneuvers as compared with standardized electrophysiological tests in the diagnosis of distal symmetrical polyneuropathy. The screening maneuvers were the 10 gram Semmes Weinstein monofilament examination (SWME), superficial pain, vibration testing by the on off method, and vibration testing by the timed method. The study population consisted of 478 subjects who were assessed by at least seven different examiners during a 4 to 5 hour stay in a diabetic neuropathy research clinic located in Toronto, Canada. The study found that the four simple screening maneuvers reveal similar operating characteristics. Cutoff points by receiver operating characteristic (ROC) curve analyses reveal that a positive or abnormal test is represented by five incorrect responses of eight stimuli applied. A negative or normal test is represented by one or fewer incorrect responses of sight stimuli applied. By these criteria, the point estimates of the positive likelihood ratios for vibration testing by the on off method, vibration testing by the timed method, the SWME, and superficial pain sensation test were 26.6, 18.5, 10.2, and 9.2, respectively. The point estimates of the negative likelihood ratios were 0.33, 0.51, 0.34, and 0.50, respectively. The screening tests showed comparable sensitivity and specificity results. The article concludes that the SWME, superficial pain test, and vibration testing by the on off method are rapid, with each requiring approximately 60 seconds to administer. The timed vibration test takes longer, and the interpretation is more complicated. The combination of two testing modalities does not improve the operating characteristics of screening from the data in this study. 1 figure. 5 tables. 36 references. (AA-M).

- **Guidelines for the Diagnosis and Outpatient Management of Diabetic Peripheral Neuropathy**

  Source: Diabetes Reviews. 7(4): 237-244. 1999.

  Contact: Available from American Diabetes Association, Inc. 1701 North Beauregard Street, Alexandria, VA 22311. (800) 232-3472.

  Summary: This article provides guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy. These guidelines were developed from an international consensus meeting attended by diabetologists, neurologists, primary care physicians, podiatrists, and diabetes specialist nurses. Diabetic peripheral neuropathy is defined as the presence of symptoms or signs of peripheral nerve dysfunction in people who have diabetes, after exclusion of other causes. The guidelines outline the components of an annual examination of a person who has diabetes and provide recommendations on methods of assessment and management of diabetic peripheral neuropathy and patient education. Assessment guidelines focus on obtaining a patient history; examining the patient, including inspecting the feet and conducting neurological and vascular examinations; performing other investigations; and identifying the at risk foot. Management guidelines focus on education of patients who do not have clinical neuropathy and those who have stage 2 clinical neuropathy and referral of patients who have stage 3 neuropathy. The guidelines use a question and answer format to provide information about who should provide patient education, what methods should be used, and what elements should be included in an education program. Although the guidelines are intended to be used by physicians involved in the outpatient management of people who have diabetes, they emphasize the concept of a multidisciplinary diabetes footcare team. 2 appendices. 4 tables. (AA-M).

- **Endocrinologic Cause of Peripheral Neuropathy: Pins and Needles in a Stocking-and-Glove Pattern and Other Symptoms**

  Source: Postgraduate Medicine. 102(2): 81-82, 90-92, 102-106. September 1997.

  Contact: Available from McGraw-Hill, Inc. 1221 Avenue of the Americas, New York, NY 10020. (612) 832-7869.

  Summary: This article reviews the endocrinologic causes of peripheral neuropathy. The authors note that diabetes is the most common cause of peripheral neuropathy in the Western world. Topics include diabetic neuropathy and its forms, diagnostic evaluation, and treatment approaches. Forms of diabetic neuropathy include distal symmetric polyneuropathy, autonomic neuropathy, diabetic neuropathic cachexia, hyperglycemic neuropathy, treatment-induced diabetic neuropathy, Bruns-Garland syndrome, cranial neuropathy, truncal neuropathy, and entrapment neuropathy. Roughly 75 percent of diabetic neuropathies are distal symmetric polyneuropathy. Treatment approaches include controlling glucose level, improving nerve function, controlling inflammation, and relieving symptoms. In addition, treatment information specific to autonomic neuropathy, thyroid-related neuropathy, and acromegaly-related neuropathy is provided. The authors note that the treatment of underlying disease is the most successful management approach. For example, tight glucose control in people with diabetes, thyroid hormone replacement therapy in people with hypothyroidism, and removal of the pituitary adenoma in people with acromegaly are advantageous. Two sidebars address hypotheses on the development of diabetic neuropathy and hypotheses on the causes of pain in diabetic neuropathy. 1 table. 21 references. (AA-M).

- **Recognizing Peripheral Neuropathy: How to Read the Clues to an Underlying Cause**

  Source: Postgraduate Medicine. 102(2): 71-72, 75, 80. September 1997.

  Contact: Available from McGraw-Hill, Inc. 1221 Avenue of the Americas, New York, NY 10020. (612) 832-7869.

  Summary: This review article provides health professionals with information about recognizing peripheral neuropathy. The author notes that peripheral neuropathy, which affects sensory, motor, or autonomic nerves, is one of the most common neurologic disorders seen in primary care. Several systemic diseases, such as diabetes, rheumatoid arthritis, and thyroid disease, can cause symptoms of peripheral nerve dysfunction. Topics include physical findings, sensory nerve dysfunction, motor nerve dysfunction, autonomic nerve dysfunction, signs and symptoms, family history, exposure history, medical history, and laboratory evaluation. The author points out that the patients' descriptions of symptoms and their onset, specific deficits found on physical examination, and family and medical history can provide clues to the cause of neuropathy. Complements to clinical evaluation may include nerve-conduction studies, electromyography, and, when necessary, nerve biopsy. A sidebar provides tips for improving clinical examination for peripheral neuropathy. 1 table. 1 reference. (AA-M).

- **Psychological Aspects of Diabetic Peripheral Neuropathy**

  Source: Diabetes Reviews. 7(4): 387-394. 1999.

  Contact: Available from American Diabetes Association, Inc. 1701 North Beauregard Street, Alexandria, VA 22311. (800) 232-3472.

  Summary: This review article summarizes the data on the psychosocial aspects of diabetic peripheral neuropathy (DPN), focusing on quality of life (QoL) and related issues and psychosocial determinants of adherence or nonadherence to preventive foot care. Despite a proliferation of psychosocial and behavioral studies in diabetes, complications, including DPN, have to date been largely neglected. The few reports that have assessed the effects of complications on the well being of patients, their physical functioning, and their QoL rarely addressed neuropathy in isolation. When DPN was addressed, several problems existed. First, the neuropathy itself was poorly defined. Second, studies predominantly used generic approaches and rarely offered any clinically meaningful data on the impact of DPN on psychosocial functioning. Third, researchers tended to focus on extreme manifestations of DPN such as severe pain, foot ulcers, and amputations, whereas the majority of neuropathic patients do not fall into these categories. Until recently, research into the psychosocial variables that might influence adherence or nonadherence to preventive foot care was not driven by any integrated theory and, therefore, lacked explanatory power as to how behavioral decisions were made. There is now some progress in this area. A new generation of measures, that is, condition specific measures, are in development, such as NeuroQo9L, a neuropathy specific measures. Current research that is guided by the Illness Perception Approach appears promising in explaining adherence or nonadherence to preventive foot care. Newly emerging patient centered, neuropathy focused, theoretically based approaches to adherence behaviors and QoL should increase clinicians' understanding as to how patients who have diabetes experience and deal with their neuropathy. This research should improve the ability to empower patients to manage their neuropathy more efficiently, ultimately leading to better physical and psychosocial outcomes. 1 figure. 60 references. (AA-M).

- **Diabetic Peripheral Neuropathy: New Approaches to Treatment, Classification, and Staging**

  Source: Diabetes Spectrum. 6(4): 233-257. July-August 1993.

  Contact: Available from American Diabetes Association. 1701 North Beauregard Street, Alexandria, VA 22311. (800) 232-3472. Website: www.diabetes.org.

  Summary: This special section of Diabetes Spectrum reviews and summarizes recent articles elucidating new approaches to the treatment, classification, and staging of diabetic neuropathy. One main article concerns strategies for using patient education to translate research findings in peripheral neuropathy; another describes a research study investigating the use of Tolrestat for mild diabetic neuropathy. Summary and commentary articles discuss the effects of uridine in the treatment of diabetic neuropathy; the relationship between sural nerve morphometric findings and measures of peripheral nerve function in mild diabetic neuropathy; the effects of pancreas transplantation on diabetic neuropathy; the peripheral neuropathy profile in various groups of people with diabetes; severe early-onset polyneuropathy in IDDM; acute and remitting painful diabetic polyneuropathy; the effect of treatment with capsaicin on daily activities of patients with painful diabetic neuropathy; the Rochester Diabetic Neuropathy Study; and hypoxic neuropathy and its relevance to human diabetic neuropathy.

- **Peripheral Neuropathy in Patients with Chronic Renal Failure: A Treatable Source of Discomfort and Disability**

  Source: Postgraduate Medicine. 102(4): 249-250, 255-257, 261. October 1997.

  Contact: Available from McGraw-Hill, Inc. 1221 Avenue of the Americas, New York, NY 10020. (612) 832-7869.

  Summary: Years ago, patients with chronic renal failure (CRF) usually died early. Central nervous system manifestations (e.g., seizures, coma) attracted the most attention, and signs of neuropathy were often overlooked. After use of long term hemodialysis became widespread, patients began to live longer, and neuropathy began being reported more often. This article describes typical presentations of the most often seen types of neuropathy in these patients: uremic polyneuropathy, mononeuropathies, and associated contributory conditions. The authors summarize signs and symptoms, diagnosis, and the therapeutic approach for uremic polyneuropathy, then briefly discuss the other two conditions. Treatment options for uremic polyneuropathy include hemodialysis, renal transplantation, and symptomatic medical therapy. Hemodialysis or peritoneal dialysis halts the progress of polyneuropathy but usually does not bring improvement. However, improvement invariably occurs with successful renal transplantation. Long term followup has shown that successful renal transplantation has a less favorable effect on uremic polyneuropathy in diabetic patients, probably because diabetes is an additional contributory process. 15 references. (AA-M).

## Federally Funded Research on Peripheral Neuropathy

The U.S. Government supports a variety of research studies relating to peripheral neuropathy. These studies are tracked by the Office of Extramural Research at the National

Institutes of Health.[2] CRISP (Computerized Retrieval of Information on Scientific Projects) is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other institutions.

Search the CRISP Web site at **http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen**. You will have the option to perform targeted searches by various criteria, including geography, date, and topics related to peripheral neuropathy.

For most of the studies, the agencies reporting into CRISP provide summaries or abstracts. As opposed to clinical trial research using patients, many federally funded studies use animals or simulated models to explore peripheral neuropathy. The following is typical of the type of information found when searching the CRISP database for peripheral neuropathy:

- **Project Title: A MURINE MODEL OF SMITH-MAGENIS SYNDROME**

  Principal Investigator & Institution: Boerkoel, Cornelius F.; Molecular and Human Genetics; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 77030

  Timing: Fiscal Year 2001; Project Start 01-SEP-1999; Project End 31-AUG-2004

  Summary: Smith-Magenis syndrome (SMS) is a multiple congenital anomaly mental retardation syndrome associated with a heterozygous deletion of human chromosome l7p11.2. This microdeletion syndrome has an estimated birth incidence of 1 in 20-25,000, making it one of the most frequently observed chromosomal deletions in humans. Clinical features include mental retardation, **peripheral neuropathy,** short stature, minor craniofacial anomalies, short fingers, microcornea, developmental defects of the heart and kidneys, and neurobehavioral abnormalities. The complex phenotype suggests deletion of several contiguous genes and is hypothesized to result from haploinsufficiency. Although several genes have been identified in the SMS common deletion interval, their contribution to this complex phenotype remains speculative. Chromosome 17p11.2 is syntenic to the 32-34 cM region of murine chromosome 11. Several genes have been mapped to both the mouse and human regions of synteny. Other genes in l7p11.2 also likely have murine homologues. This proposal seeks to characterize which gene or group of genes is responsible for SMS by using chromosome engineering to construct deletions of those regions of mouse chromosome 11 that are syntenic for the human SMS deletion interval. Extensive characterization of the engineered mice will then be performed to determine the consequences of gene haploinsufficiency. These analyses will contribute to the understanding of the molecular basis of the SMS chromosomal microdeletion syndrome and will have potent implications for human development and biology. The career development aims of this proposal have been designed to provide the candidate with the tools necessary for human disease gene identification and analysis as well as with the capability of developing murine models of human disease. Baylor College of Medicine provides an environment that is unparalleled for developing murine models and that is ideally suited to prepare highly motivated individuals for careers in academic medicine. The Mentored Scientist Development Award would further facilitate this process.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

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[2] Healthcare projects are funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDCP), Agency for Healthcare Research and Quality (AHRQ), and Office of Assistant Secretary of Health (OASH).

- **Project Title: A NEW DEVICE FOR MONITORING DIABETIC MICROCIRCULATION**

  Principal Investigator & Institution: Drost, Cornelis J.; Transonic Systems, Inc. 34 Dutch Mill Rd Ithaca, Ny 14850

  Timing: Fiscal Year 2003; Project Start 01-SEP-2003; Project End 31-AUG-2004

  Summary: (provided by applicant): Diabetes-related microcirculation problems result in 200,000-foot ulcer cases and 80,000 amputations per year in the USA alone. Screening could lead to early detection, treatment and prevention. Transonic proposes to develop a laser Doppler-based tissue perfusion monitor, optimized for screening peripheral neuropathy-induced microcirculation deficiencies. This novel monitoring system will enable research studies of deficiencies in peripheral blood perfusion and neurological control of perfusion during early stages of diabetes. On a longer horizon, such studies may produce a simple, non-invasive test for early detection of diabetes using a laser Doppler tissue perfusion monitor as developed under this proposal. The proposed approach has a high likelihood of success. The novel monitor derives from our existing commercial laser Doppler monitor, with technology enhancements to optimize measurement accuracy under the low perfusion conditions of diabetic disease. A clinical connection between diabetes mellitus and changes in the frequency spectrum of Doppler tissue perfusion signals has been demonstrated by our Phase I clinical collaborators. During Phase I we will build prototype hardware to demonstrate feasibility of our novel approach to high-resolution laser Doppler flowmetry under low flow conditions, and spectral analysis software optimized for low-frequency skin perfusion measurement. Our Wake Forest Medical College collaborators will validate the adequacy of this hardware and software in a clinical setting. Phase II funding will support clinical studies by three independent research groups on diabetic populations, while we develop research-grade hardware and analysis software to be marketed worldwide upon conclusion of the grant.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ABT378/RITONAVIR WITH RT INHIBITORS IN ANTIRETROVIRAL NAIVE HIV INFECTED PATIENTS**

  Principal Investigator & Institution: Hicks, Charles B.; Duke University Durham, Nc 27706

  Timing: Fiscal Year 2001

  Summary: Purpose: The main objectives of the study are to assess the safety, tolerability, and antiviral activity of ABT-378/ritonavir and to determine the steady-state pharmacokinetic profile of the combination in healthy, treatment-naive, adult HIV-infected males and females. ABT-378 is an HIV-1 protease inhibitor being developed by Abbott Laboratories which has approximately 10-fold greater in vitro potency than ritonavir and is active against ritonavir-resistant isolates; but ABT- 378 demonstrated poor bioavailability in pre-clinical trials. Co-administration of ABT-378 with ritonavir, however, substantially improves the pharmacokinetic profile of ABT-378. This is attributable to the inhibition of ABT-378 metabolism by ritonavir. Methods: Protocol M97-720 is a Phase I/II, randomized, ABT-378 dose-blinded, multi-center study of oral ABT-378/ritonavir in combination with two marketed reverse transcriptase inhibitor antiretroviral agents [stavudine (d4T) and lamivudine (3TC)] in approximately thirty-two healthy, treatment-naive, adult HIV- infected males and females. On Day -1 patients will be equally randomized to one of two blinded treatment arms: i) 200 mg ABT-378/100 mg ritonavir Q12H and ii) 400 mg ABT-378/100 mg ritonavir Q12H. All

patients will add stavudine (d4T) and lamivudine (3TC) to their ABT-378/ritonavir regimen on Day 22. Study drug administration will begin with ABT-378/ritonavir on Study Day 1. All doses of study drug will be directly observed by study personnel (in the GCRC) for Study Days 1-14. After Study Day 14, follow-up visits will be planned for Study Days 16 and 18, Day 21 (Week 3), and Day 28 (Week 4). Following Day 28, visits will be scheduled biweekly until Week 12 and monthly, thereafter. Measurements of vital signs, physical examinations, ECGs, routine clinical laboratory evaluations, determinations of antiviral activity, and quality of life questionnaires will be repeated at regularly scheduled intervals. Blood samples for determination of plasma levels of ABT-378 and ritonavir plasma levels and protein binding will also be obtained. Any patient who discontinues ABT-378/ritonavir will be followed at regularly scheduled study visits for 60 days after the last dose of ABT-378/ritonavir. Results: Twelve male HIV-seropositive subjects have enrolled in the trial. One subject dropped out of the trial after the first visit and has been lost to follow-up. The other eleven subjects have continued to take the study medication and have had increases in CD4 counts and sustained HIV-1 viral suppression below the limits of detection. Two of the eleven subjects have developed some **peripheral neuropathy.** Four serious adverse events have been reported among the eleven subjects (a mitral valve replacement, a post-surgical ileus, dependence on narcotics, and chest pain, which was found to be gastrointestinal in nature). None of the subjects who experienced serious adverse events had to discontinue the trial, and all have continued to respond well to the study medication. The most common side effects related to the study medication have been loose stools and diarrhea. The most common laboratory abnormalities have been increases in serum cholesterol and triglycerides, which are side effects common to other protease inhibitors. Based on data collected thus far, the study medication appears to be safe, well-tolerated, and effective in suppressing HIV-1 RNA levels below the limits of detection. Significance: Safe, well-tolerated medications that lead to sustained HIV-1 viral suppression to undetectable levels have the potential to decrease stress on the immune system, resulting in higher CD4+ cell counts, longer disease-free survival time, and improved quality of life for people with HIV infection. Future Plans: All subjects in the study will continue to receive study medication beyond the initial 12-month trial, with laboratory evaluation every 3 months. The pharmaceutical sponsor plans to continue to provide the medication to all subjects until either the drug is approved by the FDA or development is discontinued.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ACHILLES TENDON LENGTHENING ON PATIENTS WITH DIABETES**

  Principal Investigator & Institution: Mueller, Michael J.; Associate Professor; Physical Therapy Education; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

  Timing: Fiscal Year 2001; Project Start 17-AUG-1998; Project End 31-MAY-2003

  Summary: (Adapted from the Applicant's Abstract): Patients with diabetes mellitus (DM) and **peripheral neuropathy** are at high risk for forefoot plantar ulcers and subsequent lower extremity amputation. Total contact casting currently is the most effective treatment for healing neuropathic plantar ulcers but ulcer recurrence is high (30-50%) when patients discontinue casting and resume walking. An equinus deformity (limited ankle dorsiflexion range-of-motion [ROM]) is associated with these recurrent ulcers. Although descriptive evidence indicates an Achilles lengthening procedure (which corrects the equinus deformity) can improve healing rates in chronic ulcers, there

have been no controlled trials. The primary purpose of this study will be to conduct a randomized prospective controlled trial to determine if percutaneous Achilles lengthening and total contact casting is more effective than total contact casting alone to heal forefoot plantar ulcers. Secondary purposes are to determine the effects of casting and percutaneous Achilles lengthening on measures of impairments, functional limitations, and disability in patients with DM and **peripheral neuropathy.** The specific aims of this project are to determine the effect of the Achilles lengthening procedure on patients with DM, **peripheral neuropathy,** a forefoot ulcer, and an equinus deformity in regards to 1) Wound healing, 2) Impairments (dorsiflexion range-of-motion, plantar flexor muscle performance), 3) Functional Limitations (Physical Performance Test, Functional Reach, walking ability), and 4) Disability (SF36). The results will have important implications for prevention of wound infection and lower extremity amputation; and improvement in impairments, functional limitations, and disability in this group of high risk patients with chronic disease.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ADHESION AND GENE EXPRESSION IN CMT1B**

  Principal Investigator & Institution: Shy, Michael E.; Associate Professor of Neurology; Neurology; Wayne State University 656 W. Kirby Detroit, Mi 48202

  Timing: Fiscal Year 2001; Project Start 05-APR-2001; Project End 31-MAR-2005

  Summary: (provided by applicant): Myelin is a multi-lamellar structure that surrounds axons in both the CNS and PNS facilitating nerve conduction. P0, a transmembrane glycoprotein of the immunoglobulin super family, is the major structural protein in PNS myelin, and is expressed exclusively in Sehwann cells, the myelinating glia. Human mutations in P0 give rise to peripheral demyelinating neuropathies. Our long range goal is to understand the role of P0 in myelination and disease. Several lines of evidence demonstrate that P0 acts as a homophilic adhesion molecule, suggesting that P0 mediates myelin compaction through homophilic interactions between adjacent membrane leaflets. Analysis of the crystal structure of the P0-extracelfular domain indicates that adjacent P0 molecules have the potential to interact in cis to form tetramers, and that these tetramers may further interact in trans to mediate homophilic adhesion. Furthermore, mutations of amino acid residues that the crystal structure identifies as critical to both cis and trans interactions cause a demyelinating **peripheral neuropathy** in patients. Mutations within the cytoplasmic domain of P0 are also found in patients with inherited demyelinating neuropathy and deletions within the cytoplasmic domain have been experimentally shown to result in loss of adhesive function. We have shown that point mutations of serine and threonine in a consensus Protein Kinase C binding site, as well as a second nearby serine, which corresponds to a human nonsense mutation giving rise to demyelinating neuropathy, are critical to adhesive function. Furthermore, our deletion analysis suggests that the juxtamembrane cytoplasmic region is also important for adhesive function. Thus both the extracellular and intracellular domains of P0 are necessary for homophilic adhesion in vitro and for myelination in vivoadhesion. P0 may also play a regulatory role during myelination. Complete loss of P0 in mice through homologous recombination not only produces a demyelinating **peripheral neuropathy,** but also markedly alters the pattern of myelin-specific gene expression in peripheral nerve. However, the relationship between adhesive function and this regulatory function is not known. In this proposal we will further define the regions and specific residues in the extracellular and intracellular domains that are essential for adhesive function through expression of mutated P0 in

established cell lines and analysis of P0-mediated, as well as attempt to resolve the relationship between the seemingly separate P0 functions, adhesive and myelination.

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- **Project Title: ANTIOXIDANT STRATEGIES FOR PARKINSON'S DISEASE**

  Principal Investigator & Institution: Schor, Nina F.; Professor and Chief of Child Neurology; Children's Hosp Pittsburgh/Upmc Hlth Sys of Upmc Health Systems Pittsburgh, Pa 15213

  Timing: Fiscal Year 2002; Project Start 01-JUL-2002; Project End 30-JUN-2006

  Summary: (provided by applicant): Reactive oxygen species (ROS) have been implicated in the pathogenesis of Parkinson's disease. This suggests that antioxidant strategies may be useful in the treatment and/or prevention of this neurodegenerative disorder. We have developed and implemented two models for the central movement disorder and autonomic **peripheral neuropathy,** respectively, associated with Parkinson's disease. We propose to use these models to design and test antioxidant strategies we have previously developed for adjunctive use with ROS-generating chemotherapeutic agents. We will further use our studies of the biochemical effects of antioxidant treatment to develop a screening test for new antioxidant agents for use in Parkinson's disease and other ROS-related disorders. Specifically, we propose to test the hypothesis that recycling antioxidants increase expression of p21 wafl/cip1,enhance binding of HIF-1 and CREB to DNA, activate NF-kappaB, prevent ROS-induced morphological apoptosis, and decrease ROS-induced membrane phospholipid and protein nitration in culture models of Parkinson's disease. We will further test recycling antioxidants for their distribution to the CNS and peripheral compartments, and use this information to test CNS-penetrating and non-CNS-penetrating agents for efficacy in the central and autonomic nervous system models, respectively, of Parkinson's disease. Finally, we will test the hypothesis that the magnitude of induced in vitro biochemical change for each drug correlates with the degree of protection from the effects of ROS in the CNS or autonomic model. This latter study will pave the way for development of an in vitro screening test for new antioxidant strategies proposed for use in Parkinson's disease. This application specifically addresses the NINDS agenda for research in Parkinson's disease in its development of in vitro screening tests for putative therapeutic agents in general and antioxidants in particular for this disease, its development of animal models for the clinical aspects of Parkinson's disease, and its potential for further elucidation of the mechanisms of ROS-induced apoptosis in the nervous system.

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- **Project Title: ANTIVIRAL NUCLEOSIDE-INDUCED NEUROPATHIC PAIN MECHANISMS**

  Principal Investigator & Institution: Levine, Jon D.; Professor of Medicine; Oral and Maxillofacial Surgery; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 94122

  Timing: Fiscal Year 2001; Project Start 30-SEP-2001; Project End 31-JUL-2005

  Summary: (provided by applicant): Anti-retroviral nucleoside analogs are widely used in the treatment of AIDS. However, anti-retroviral nucleoside therapy often must be discontinued because it induces a debilitating painful **peripheral neuropathy** for which no adequate therapy is available. To facilitate the rational design of pharmacological strategies to treat or prevent nucleoside-induced neuropathic pain, we will perform a series of experiments to elucidate the cellular mechanisms of nucleoside-induced painful

neuropathy. Specifically, we will establish a model of painful **peripheral neuropathy** induced by anti-retroviral nucleosides in the rat. We will then analyze nucleoside-induced changes in the excitability of nociceptive nerve fibers in this model. Guided by that analysis, we will employ patch-clamp recording of cultured sensory neurons to study the effects of antiretroviral nucleosides on specific transduction molecules and ion channels. Those studies will establish a behavioral and cellular model of anti-retroviral nucleoside-induced painful neuropathy that will enable our proposed experiments to investigate intracellular second messenger systems and ion channels that produce the nucleoside-induced hyperalgesia and nociceptor hyperexcitability. Because nucleoside-induced neuropathy can be exacerbated by common comorbidities in this population of patients, including neuropathies induced by diabetes mellitus, and alcoholism, we will also evaluate interactions between nucleoside-induced neuropathy and these comorbid neuropathies. Our laboratory has extensive expertise in the full range of in vivo and in vitro methods to be employed, has successfully developed experimental models of **peripheral neuropathies,** and has performed investigations of second messengers involved in models of painful **peripheral neuropathies** induced by diabetes, alcohol, and vincristine, and in inflammatory hyperalgesic states. In addition to their great potential clinical significance, these studies should also provide basic insights into cellular mechanisms controlling neuronal excitability.

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- **Project Title: AXONAL TRANSPORT AND PERIPHERAL NERVE FUNCTION**

  Principal Investigator & Institution: Topp, Kimberly S.; Medicine; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 94122

  Timing: Fiscal Year 2001; Project Start 01-FEB-1997; Project End 31-JAN-2003

  Summary: (Adapted from the Applicant's Description): Over the course of a lifetime, a significant percentage of the population needs medical attention for some form of neuropathy, such as low back pain, diabetic neuropathy or carpal tunnel syndrome. Due to their prevalence and complexity of treatment, neuropathies have a major financial impact in health care. Compromise of axonal transport may contribute to the pathophysiology of several clinical neuropathies. The goal of the candidate's proposed research is to understand the role of axonal transport in peripheral nerve function. Axons are dependent on continuous replenishment of membrane proteins and on the feedback provided by materials taken up at nerve terminals. The length of the nerve dictates that bi-directional transport be tightly regulated. Interruption of axonal transport leads to Wallerian degeneration of axons distal to the site of impairment. Therefore, several neuropathies are thought to have impaired axonal transport. However, there have been few controlled investigations of the functional consequences of impaired axonal transport or of the aspects of transport that may contribute to **peripheral neuropathy.** The proposed specific aims address these two issues, and seek to identify physical interventions that may alter function in neuropathic nerves. The first aim is to determine how the function of peripheral nerves is impaired by disruption of axonal transport. To accomplish this aim, peripher-al nerves in which axonal transport has been experimentally impaired will be tested for their ability to respond to sensory stimuli, using behavioral tests and electrophysiological techniques. The second aim is to determine what aspects of axonal transport are disrupted in **peripheral neuropathies.** To address this aim, peripheral poly- or mononeuropathy will be experimentally induced, and anterograde or retrograde axonal transport will be tested for impairment, using biochemical and morphological techniques. Additional observations will be made of the components required for axonal transport, specifically, energy stores, divalent

cations and cytoskeletal structural framework. The third aim is to identify physical interventions that improve or impair axonal transport and nerve function in **peripheral neuropathies.** To accomplish this aim, neuropathic nerves with demonstrated alterations in axonal transport will be further exposed to nerve compression, extremity mobilization or immobilization. Nerve function will be assessed using behavioral tests and electrophysiological techniques.

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- **Project Title: BASIS OF VOLTAGE & CHEMICAL GATING IN CONNEXIN CHANNELS**

  Principal Investigator & Institution: Puljung, Michael C.; Pharmacological & Physiol Scis; University of Chicago 5801 S Ellis Ave Chicago, Il 60637

  Timing: Fiscal Year 2001; Project Start 30-SEP-2001

  Summary: Gap junction channels, dodecamers of connexin proteins, provide direct coupling between the cytoplasm of adjacent cells, each cell contributing a hexameric connexon, or hemichannel. Mutations in connexin genes are associated with diseases including X-linked Charcot-Marie-Tooth disease (CMTX), a **peripheral neuropathy** caused by defects in connexin32. The applicant aims to characterize the pharmacology of conducting hemichannels formed by human connexin37 (hCx37) and bovine connexin44 (Cx44), which have diverse properties with respect to gating. Experiments are proposed to test the hypothesis that block of these hemichannels by heptanol, halothane, and divalent cations should be the same in hemichannels as in intact intercellular channels, indicating that gap junctional uncoupling is due to hemichannel block. Voltage effects on divalent block will also be assessed. Single channel currents for hCx37 will determine whether the hemichannel currents have a role under physiological conditions. Native preparations will be used to further explore this possibility. Finally, chimeric channels, containing domains of the hCx37 and U44, will be made to determine the molecular basis of gating. Chemical gating properties will be assessed in chimeric hemichannels that exchange the cytoplasmic loop and carboxy-terminal domains, regions implicated in chemical gating of connexins. Voltage gating properties will be examined in hemichannels and intercellular channels formed by chimeras that exchange the extracellular loop domains. Site-directed mutants can also be made in the domains involved in gating. Once the molecular basis of gating is identified, specific residues may be used as targets for rationale drug design to treat illnesses like CMTX.

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- **Project Title: CELLULAR EVENTS IN HERITABLE PERIPHERAL NEUROPATHIES**

  Principal Investigator & Institution: Notterpek, Lucia M.; Neuroscience; University of Florida Gainesville, Fl 32611

  Timing: Fiscal Year 2001; Project Start 15-JUL-2001; Project End 30-JUN-2005

  Summary: (provided by applicant): Heritable-demyelinating neuropathies with an estimated incidence of 1:2,500 in the general population, including Charcot-Marie-Tooth disease type 1A (CMT1A), account for a significant portion of peripheral nerve disorders leading to muscle atrophy and functional impairment. Advances in human genetics have led to the identification of specific gene defects associated with a large fraction of inherited neuropathies, however the cellular athogenesis elicited by the genetic alterations is not well understood. In the majority of CMT1A patients the peripheral myelin protein 22 (PMP22) gene on chromosome 17 is duplicated, while in a smaller but significant fraction, single point mutations in PMP22 have been identified.

Morphological studies of CMT1A nerve biopsies revealed abnormal intracellular accumulation of PMP22 in the Schwann cell cytoplasm and in the endoneurial tissue. Cell culture studies show changes in the intracellular trafficking of mutant PMP22s, and intracellular retention of the overproduced wild-type protein in newly defined cytoplasmic inclusions, termed aggresomes. How altered intracellular trafficking of the mutant or overproduced PMP22 triggers the cascade of events leading to nerve pathology is not known. The hypothesis of this research application is that the changes in intracellular glial protein trafficking alter the biochemical integrity of the Schwann cell membrane, thus have a direct role in initiating the pathogenesis of the neuropathies. The aim of the project is to understand the mechanisms underlying the changes in PMP22 localization in CMT1A Schwann cells and to identify potential targets for therapeutic interventions. Experiments will be performed at the subcellular level in myelinating cocultures of neuropathy Schwann cells and peripheral neurons, as well as in ex vivo neuropathy nerve preparations. The turnover rate and the subcellular trafficking of PMP22 and other myelin proteins, including protein zero, will be determined biochemically and morphologically, with and without the use of pharmacological agents known to affect specific steps in protein processing. Particular emphasis will be placed on evaluating the involvement of the ubiquitin-proteasome, protein degradative, pathway in the regulation of PMP22 protein turnover. In depth understanding of the cellular mechanisms of pathogenesis in **peripheral neuropathies** is essential for the future design of effective pharrnacological therapies.

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- **Project Title: CHARACTERIZATION OF A NOVEL CNS SPECIFIC CONNEXIN, CX29**

  Principal Investigator & Institution: Altevogt, Bruce M.; Neurobiology; Harvard University (Medical School) Medical School Campus Boston, Ma 02115

  Timing: Fiscal Year 2001; Project Start 01-JUL-2001

  Summary: (As provided by Applicant): Gap junctions are collections of intercellular channels permeable to molecules less than 1 kDa, which play an important role in both electrical and chemical communication in cells of the central nervous system (CNS). The importance of gap junctions in the nervous system is underscored by the observation that connexin mutations are responsible for common heritable diseases affecting the CNS and peripheral nervous system (PNS). For example, mutations of connexin (Cx) 26 account for more than half of all cases of genetic deafness, affecting more than 1 in 2000 children. Mutations in Cx32 are responsible for the second most common inherited **peripheral neuropathy,** X-linked Charcot Marie Tooth disease (CMTX). CMTX affects the myelination of axons in the PNS, but surprisingly although oligodendrocytes abundantly express Cx32, there are no convincing reports that CNS myelin is affected in CMTX. It is believed that this may be due to functional gap junctions between oligodendrocytes and astrocytes. However, the connexins that are expressed in astrocytes and oligodendrocytes are not capable of forming functional channels. The purpose of this proposal is to further characterize Cx29, analyze functional coupling between oligodendrocytes and astrocytes, and determine what connexins are responsible for this coupling. I will perform dye transfer studies on spinal cord slices from adult mice to study glial coupling in the mature CNS. In addition, I will determine which connexins are expressed in oligodendrocytes and astrocytes. Once I have determined the protein localization of every known glial connexin, I will examine the channel properties of the identified connexins utilizing the paired Xenopus-oocyte system.

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- **Project Title: CHROMIUM ANALYSIS AND DIABETES**

  Principal Investigator & Institution: Paul, Kenneth G.; Biophysics Assay Lab, Inc. (Biopal, Inc) 80 Webster St Worcester, Ma 016031914

  Timing: Fiscal Year 2002; Project Start 15-SEP-2002; Project End 31-MAR-2003

  Summary: (provided by applicant): Diabetes is one of the most costly health problems in America and the seventh leading cause of death Chromium has been implicated in the regulation of insulin metabolism and a number of the signs and symptoms of diabetes are shared in common with demonstrated chromium deficiency These include impaired glucose tolerance, fasting hyperglycemia, glucosuria, hypoglycemia, elevated circulating insulin, decreased insulin receptor number, and **peripheral neuropathy** The Office of Dietary Supplements (ODS), the National Center for Complementary and Alternative Medicine (NCCAM), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) have invited applications for basic and clinical studies of the role of chromium as adjuvant therapy in type 2 diabetes and/or impaired glucose tolerance Studies report that chromium supplementation may improve diabetes control but one of the major obstacles in evaluating the biological effects of chromium involves assessing chromium status by a simple, readily available analytical method BioPAL, utilizing neutron activation analysis (NAA), proposes to develop a nonradioactive, convenient, and standardized commercial assay for chromium in biological tissues and fluids free of the problems of complicated sample preparation and potential contamination encountered with presently used techniques Our long-term goal (Phase II) is to develop advanced technology to significantly, improve the lower-limits of sensitivity for chromium as compared to current methods, including current NAA methods The assessment of chromium levels and their relationship to insulin sensitivity as well as the possible value of chromium in the control of hypoglycemia and various other symptoms associated either with diabetes or related pathologies would be not only a valuable tool in research but a means for determining individual chromium levels by a routine, non-destructive and non-invasive technique Ultimately these methods could be developed into a simple kit for use by clinicians or even individuals Similar methods can be adapted for the determination of other trace metals from the same sample in a single analysis.

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- **Project Title: CIRCUMFERENTIAL NEUROPATHIC FOOT PROTECTOR SYSTEM (CNEP)**

  Principal Investigator & Institution: Jensen, Jeffrey L.; Medical Director; Medefficiency, Inc. 4600 Hale Pkwy, Ste 440 Denver, Co 80220

  Timing: Fiscal Year 2001; Project Start 29-SEP-2001; Project End 31-MAR-2002

  Summary: Diabetic foot complications result in over 67,000 lower extremity amputations annually and cause more hospitalizations than any other single complication of diabetes. Foot wounds precede 84% of these amputations and usually occur when patients with diabetes have **peripheral neuropathy** and cannot feel foot trauma from ground-reactive (shock) and shearing (friction) forces. This loss of sensation presents a footwear challenge - to prevent wounds - current technologies don't adequately address. Currently, the most effective method for preventing foot wounds involves (1) custom molded shoes or (2) extra-depth, extra-width shoes; both with three sets of custom orthoses annually. These orthoses are expected to counteract both shock and friction, but

are insufficient. These options have serious fit and availability limitations, and significant material and labor costs. Jointly with Z-Coil, Inc. of Albuquerque, MedEffciency poses to develop the Circumferential Neuropathic Foot Protection System (CNFP) - an extra-depth, extra-width protective shoe with a custom orthosis. The shoe's patented spring technology absorbs shock, while its silicone custom orthosis minimizes friction. Utilization should increase with the ability to customize and dispense immediately with lower cost than present alternatives, resulting in fewer foot wounds, fewer amputations, reduced healthcare costs and higher quality of life for patients with diabetes. PROPOSED COMMERCIAL APPLICATIONS: In the U.S. alone, there are estimated to be over 16 million people with diabetes, with at least one-third undiagnosed. There are over 67,000 diabetic amputations each year, but the majority are avoidable with proper intervention to prevent foot wounds. Proper footwear for these patients is absolutely essential for wound prevention. If the CNFPS could capture just 10% of the high-risk market for diabetic footwear, it would generate revues in excess of $70 million each year based on Medicare reimbursement rates, while still significantly reducing total healthcare costs.

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- **Project Title: CLAUDE D PEPPER OLDER AMERICANS INDEPENDENCE CENTER**

  Principal Investigator & Institution: Halter, Jeffrey B.; Professor; Internal Medicine; University of Michigan at Ann Arbor 3003 South State, Room 1040 Ann Arbor, Mi 481091274

  Timing: Fiscal Year 2001; Project Start 01-SEP-1999; Project End 31-AUG-2004

  Summary: This is a competing renewal application for support of the Claude D. Pepper Older Americans Independence Center (OAIC) at the University of Michigan (UM Pepper Center). The specific aims of the UM Pepper Center are: 1) To enhance the independence of older people by developing and testing new interventions for common health problems causing disabilities. 2) To provide Research Resources Cores that support and assist investigator initiated research projects which can lead to new insights into the basic mechanisms underlying conditions that contribute to loss of independence of older adults. 3) To strengthen the UM environment for training of future academic leaders in geriatrics and aging. 4) To attract UM junior faculty to research on problems that limit independence of older adults and on potential interventions to enhance such independence. 5) To carry out innovative demonstration and dissemination projects to translate OAIC research findings in order to improve the independence of older adults. The UM Pepper Center has a well established leadership and administrative structure, Research Development Core (RDC), and four Research Resources Core (Human Subjects Core; Biomechanics Core; Methodology, Data Management and Analysis Core; and Core Facility for Aged Rodents). The RDC features three central elements: (1) a Pilot/Feasibility Grants program; (2) a series of 2-3 day Research Retreats; and (3) a Mentorship Program. In addition, three Intervention Development Studies (IDSs) and a Demonstration and Information Dissemination Project (DIDP) are included in this competing renewal application. The three IDSs test intervention hypotheses regarding balance training to reduce falls, use of external aids and specific exercises to compensate for impaired sensorimotor function in elderly people with **peripheral neuropathy,** and the impact of modulation of body size on disease free survival in mouse models of aging. These projects have been selected to capitalize on UM's strength in development and testing of quantitative measures of functional status, expertise in geriatric pathophysiology, and experience in the use of aging animal models. The proposed IDSs will benefit greatly from the multi-disciplinary nature of the OAIC faculty. The DIDP

will translate findings from IDSs and other OAIC activities to community based medical practice, using an existing network of geriatrics programs in Michigan communities which serve as model demonstration and training sites.

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- **Project Title: CLINICAL STEP RECORDER**

  Principal Investigator & Institution: Tarler, Matthew D.; Cleveland Medical Devices, Inc. 11000 Cedar Ave, Ste 130/461 Cleveland, Oh 44106

  Timing: Fiscal Year 2003; Project Start 01-SEP-2003; Project End 31-AUG-2004

  Summary: (provided by applicant): Patients with diabetes mellitus (DM) and **peripheral neuropathy** (PN) are at high risk for lower extremity skin breakdown and subsequent amputation. Magnitude and repetition of pressures are important indicators of skin breakdown and formation of neuropathic ulcers. Currently, there are no devices that can easily and unobtrusively measure the repetition of pressures and total weight-bearing time over a prolonged period of time (e.g., 2 weeks). The most common method of treatment of these neuropathic ulcers is off loading weight over the ulcer site using a total contact cast (TCC) or an ankle foot orthosis (AFO). The primary purpose of this grant proposal is to develop an unobtrusive, self-contained, inexpensive device that can fit inside a shoe, cast, or AFO, that will record and time stamp steps, average pressures, and weight-bearing time for "at-dsiC patients for extended periods of time. The completed Clinical Step Recorder (CSR) system will be validated with patients currently using a TCC, and subjects wearing shoes with orthotic inserts. The CSR device will have many other uses, including that of an activity monitor for patients with obesity, or the elderly, which could help assess weight-bearing activities and encourage regular physical activities.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CMT PERIPHERAL NEUROPATHY: IV. GENES AND PATHOGENESIS**

  Principal Investigator & Institution: Lupski, James; Professor; Molecular and Human Genetics; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 77030

  Timing: Fiscal Year 2002; Project Start 01-JAN-1990; Project End 31-DEC-2005

  Summary: Hereditary **peripheral neuropathies** are common human genetic conditions. These clinically and genetically heterogeneous disorders produce progressive deterioration of the peripheral nerves with secondary muscle wasting and weakness in a distal distribution. The application of molecular genetic techniques to this group of disorders has resulted in a more comprehensive understanding of peripheral nerve biology that has important clinical implications. This proposal focuses on the identification of genes, molecular genetic bases, and pathogenic mechanisms regarding the inherited **peripheral neuropathy** Charcot- Marie-Tooth disease and related disorders. Human genetic and genomic approaches, informatics applications to genome databases, expression profiling coupled with mapping of peripheral nerve- specific genes, comparative genome studies between human and nonhuman primates, and molecular studies of a large cohort of patients manifesting **peripheral neuropathies** will be utilized to extend our understanding of the human peripheral nerve neurobiology. The major hypotheses to be tested are: (i) the identification of the genes involved in rare forms of familial neuropathy will provide insights into peripheral nerve structure/function and maintenance; (ii) genes that are downstream targets of the transcription factor EGR2 are important candidates for inherited peripheral nerve

disease; (iii) structural features of the human genome may result in susceptibility to constitutional DNA rearrangements associated with disease. To address these hypotheses six specific aims are proposed. These include a continuation of the collection of rare neuropathy patients and utilizing DNA samples for such patients to identify additional "peripheral nerve disease genes" by focusing on the genes for proteins that interact with periaxin and genes which are downstream from the peripheral nerve developmental transcription factor EGR2. In addition, a novel general strategy is proposed to identify peripheral nerve- specific genes utilizing bioinformatics procedures and information from the Human Genome Project to establish both positional candidate neuropathy disease genes and a microarray for expression profiling of the peripheral nervous system. Finally, based on some of our previous studies, which have enabled the identification of structural features of the human genome important to the DNA rearrangements responsible for **peripheral neuropathy,** we will examine additional features which may result in susceptibility to DNA rearrangement as well as examine these genome architectural features during primate species to gain insights into the recent evolution of mammalian genome and its implications for genomic disorders.

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- **Project Title: CONNEXIN32 MUTATIONS IN CHARCOT-MARIE-TOOTH-X DISEASE**

  Principal Investigator & Institution: Musil, Linda S.; Assistant Scientist; None; Oregon Health & Science University Portland, or 972393098

  Timing: Fiscal Year 2001; Project Start 05-FEB-2001; Project End 31-JAN-2005

  Summary: (From the Applicant's Abstract): The X-linked form of type I Charcot-Marie-Tooth disease (CMTX) is the second most common hereditary **peripheral neuropathy** in humans. CMTX is caused by mutations in the gap junction channel protein connexin32 (Cx32) that are thought to affect its ability to mediate the radial diffusion of substances through the Schwann cell myelin sheath. CMTX is genetically as well as phenotypically heterogeneous: over 200 different defects in the coding region of the Cx32 gene have been found in CMTX patients, whose clinical symptoms range from very mild/asymptomatic to eventually becoming wheelchair-bound. Studies in transfected tissue culture cells and transgenic mice indicate that different mutations interfere with Cx32 function by distinct mechanisms: some mutants are translated inefficiently and/or degraded very quickly; others appear to affect channel function at the cell surface; and many are detected only intracellularly and act as dominant negative inhibitors of wild-type connexins. How different Cx32 mutations result in these diverse phenotypes is unknown. Our initial characterization of three CMTX-linked Cx32 point mutants in PCI2 cell transfectants revealed that each mutant was defective in folding and oligomeric assembly and underwent a distinct intracellular fate: E208K Cx32 accumulated in the endoplasmic reticulum whereas both the E186K and R142W mutants were transported to the Golgi region from which they trafficked either to lysosomes (RI42W Cx32) or back to the ER (EI86K Cx32). The goal of the proposed studies is to elucidate the molecular mechanisms by which CMTX-linked mutations affect the assembly, intracellular transport, and degradation of Cx32. These studies will be conducted in transfected tissue culture cells as well as in peripheral nerve tissue from mice expressing Cx32 mutants. Specifically, we will use molecular and cellular biological techniques to: (1) define the intracellular trafficking routes and molecular chaperone interactions of CMTX-linked Cx32 mutants; (2) identify, and test the correctability of, conformational defects in Cx32 induced by different CMTX-linked mutations; (3) elucidate the mechanisms whereby Cx32 mutants gain access to, and are degraded by, cytosolic

proteasomes; and (4) determine the molecular basis for the dominant-negative activity of some CMTX-linked mutants and identify the in vivo target of this activity in myelinating Schwann cells. These studies will elucidate the causes of phenotypic diversity in CMTX as well as provide the first molecular insights into the quality control mechanisms that govern the fidelity of connexin assembly into gap junctional channels.

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- **Project Title: CONNEXIN43--A SIGNAL TRANSDUCER IN GROWTH REGULATION**

  Principal Investigator & Institution: Lau, Alan F.; Professor; None; University of Hawaii at Manoa Honolulu, Hi 96822

  Timing: Fiscal Year 2001; Project Start 01-DEC-1990; Project End 30-APR-2004

  Summary: Connexins are transmembrane proteins that form aqueous channels, known as gap junctions, which directly interconnect the cytoplasms of adjacent cells and permit the exchange of small molecules. Gap junctions play important roles in numerous functions, including cardiac and smooth muscle function, electrotonic transmission in nerves, metabolic cooperation in avascular organs such as the lens, and in development. Recently, the disturbance of normal connexin function has been discovered in specific human diseases, such as Charcot-Marie-Tooth **peripheral neuropathy** (connexin32) and hereditary non-syndromic sensorineural deafness (connexin26). It has also been postulated that the disruption of gap junctional communication may lead to a loss of growth control that contributes to the development of human cancer. In this study, we will investigate the mechanism(s) by which tyrosine kinase oncoproteins and growth factors regulate the functions) of connexin43 by phosphorylation. We will also study the regulation of connexin43 function by putative mechanism(s) involving the interaction of Cx43 with cellular proteins. Specific Aim 1 will elucidate the role that phosphorylation plays in the regulation of connexin43 by tyrosine kinase oncoproteins and growth factors. Site directed mutagenesis and dye transfer studies will clarify the mechanism(s) by which tyrosine and serine phosphorylation of connexin43 induced by v-Src and the EGF receptor disrupts connexin43 channel permeability. Specific Aim 2 will establish if the phosphorylation-induced disruption of connexin43 channels occurs by a "particle-receptor" mechanism. This work will be accomplished by the microinjection of mutant connexin43 genes and peptides into Xenopus oocytes. Specific Aim 3 will determine the mechanism(s) and functional significance of the interactions between connexin43 and ZO-1, a tight and adherans junction associated protein, and CIP7, a novel cysteine-rich protein. These studies will utilize mutants of connexin43, ZO-1, and CIP7, together with appropriate antibodies, to study the regulation of Cx43 function, subcellular localization, and phosphorylation. We will utilize techniques such as the microinjection of fluorescent dye, confocal and electron microscopy, co-immunoprecipitation and other biochemical procedures.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CORE--NEUROTOXICOLOGY AND NEURODEGENERATIVE DISEASES FACILITY**

  Principal Investigator & Institution: Mayeux, Richard P.; Professor of Neurology, Psychiatry and e; Columbia University Health Sciences New York, Ny 10032

  Timing: Fiscal Year 2002

  Summary: Research efforts in the Neurotoxicology/Neurodegenerative Disease Research Core will be under the direction of Dr. Richard Mayeux and will span clinical,

epidemiological, and mechanistic studies of lead and mercury poisoning and neurodegenerative diseases including Parkinson s and Alzheimer?s disease. It is anticipated that Dr. Mayeux will form task-oriented working groups which will focus on specific problems within areas of interest. Members of the faculty, postdoctoral fellows and doctoral students will meet monthly to discuss topics of ongoing interest in one of the following areas: 1) gene-environment interactions in the neurodegenerative diseases of aging; 2) molecular mechanisms involved in the perturbation of iron metabolism as it relates to Parkinsonism; 3) genetic susceptibility to Parkinson s disease in first-degree relatives of both sporadic and familial cases and the pattern of inheritance; 4) the genetic bases of essential tremor and Alzheimer?s disease; 5) effects of lead on cognitive performance and development of children; 6) relationships between occupational exposure to mercury vapor and the risk of tremor, **peripheral neuropathy,** cerebellar dysfunction and measures of abnormal balance; 7) mercury exposure derived from amalgams in the mouth and possible associations with neurological dysfunction or neuropsychological deficits; 8) caloric intake, body mass index and the risk of neurodegenerative disease; 9) mitochondrial function in normal aging, Parkinson s and Alzheimer s disease; 10) occupational mercury exposure and the risk of memory and visuospatial ability and disturbed mood; 11) molecular mechanisms of lead neurotoxicity; 12) mechanisms of manganese-induced Parkinsonism; and 13) molecular mechanisms of MPTP. Task-oriented working groups will be composed of selected members of the research core, facilities cores and Center staff as needed. The framework in which these work groups will operate will be flexible and will address specific research concentrations dictated by the overall focus of the Center. The specific aims are as follows: 1) to stimulate and guide interdisciplnary research on neurodegenerative diseases; 2) to stimulate and guide research on neurotoxicology with an emphasis on the neurotoxicity of transition and heavy metals; 3) to expand mechanistic and epidemiologic studies among the elderly of Northern Manhattan and; 4) to extend research efforts concerning the interaction of genetic susceptibility markers and environmental exposures in Parkinson?s and Alzheimer?s Disease. It is anticipated that highlights of meetings held in the 12 research areas will be presented at the bi-weekly work-in-progress meetings and that these meetings will provide a vehicle for communication of progress to other members of the Center and outreach programs.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: DIABETES, PRE-DIABETES, AND FALLS IN OLDER ADULTS**

  Principal Investigator & Institution: Schwartz, Ann V.; Epidemiology and Biostatistics; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 94122

  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 30-JUN-2005

  Summary: (provided by applicant): In older adults, diabetes may increase the risk of falls and fall injuries, particularly fractures. Diabetes is also associated with lower extremity performance decline, which may contribute to fall risk and difficulty with independent living. Falls and poor lower extremity performance represent serious threats to the health and quality of life for this population, yet there has been little study of the risk factors for these outcomes among older adults with diabetes. Ultimately, trials will be needed to ascertain how these consequences can be prevented or relieved. However, more complete and conclusive data about the relationship between diabetes and risk factors for falls and declining lower extremity performance are needed. Taking measures to prevent these outcomes among older adults with impaired glucose metabolism (pre-diabetes) may also prove prudent. Studies are needed to determine if older pre-diabetic adults have a higher risk of falls and decline in lower extremity

performance and what risk factors might account for any increased risk. This group might be especially important to target for preventive interventions. The Dynamics of Health, Aging and Body Composition (HABC), a longitudinal study among 3,075 older adults (70-79 years old at baseline), provides an exceptional resource to assess the influence of diabetes and pre-diabetes on falls and lower extremity performance. HABC includes 681 participants with diabetes and 945 participants with pre-diabetes, approximately equal numbers of men and women, and African-American and white participants. Measurements of falls and lower extremity performance are being collected over five years at annual clinic visits. A wealth of information is available on potential predictors of these outcomes that are related to diabetes, including fasting glucose, HbA[lc], postural hypotension, body composition, **peripheral neuropathy,** vision, and medications. In addition, data from hospital admissions are available to investigate serious fall injuries associated with diabetes. We propose performing secondary analyses using HABC data to investigate the risk factors for falls and lower extremity performance decline among those with diabetes or pre-diabetes, emphasizing risk factors that might be a target of intervention. These analyses will inform future efforts to design trials to prevent falls and maintain strength and balance in older adults with diabetes or pre-diabetes.

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- **Project Title: DIABETIC NEUROPATHY: IMPLICATIONS FOR WOUND REPAIR**

  Principal Investigator & Institution: Gibran, Nicole S.; Associate Professor; Surgery; University of Washington Seattle, Wa 98195

  Timing: Fiscal Year 2001; Project Start 30-SEP-1999; Project End 31-AUG-2003

  Summary: Peripheral neuropathy in patients with diabetes mellitus is closely associated with development of cutaneous non-healing ulcers. Twenty to thirty thousand amputations performed annually in the United States on diabetic patients with chronic non-healing ulcers significantly impact medical costs, impairment and quality of life. Determining cellular events leading to diabetic neuropathy and impaired wound healing provides an opportunity for therapeutic intervention. We hypothesize that in patients with diabetes mellitus, microvascular endothelial cells and keratinocytes 1) do not produce necessary neurotrophic factors for sensory nerve fiber growth and 2) do not respond normally to nerve derived inflammatory mediators and these abnormalities contribute to impaired wound healing. We anticipate that hyperglycemia prevents normal signaling between cutaneous cells and sensory nerve fibers. This may result from decreased substance P due to the reduced innervation. Glycosylation of substance P, cell surface receptors or matrix molecules due to prolonged hyperglycemia may inhibit normal neuroinflammation. Alternatively, proteolytic degradation of substance P by increased levels of the enzyme neutral endopeptidase may reduce neuroinflammation. We will test our hypothesis by addressing the following: Specific Aim 1: To determine whether hyperglycemia blunts the response of cutaneous cells to substance P. We will compare substance P- induced NGF production by microvascular endothelial cells and keratinocytes under normal and hyperglycemic conditions. We will evaluate the effect of hyperglycemia on substance P-induced changes in endothelial cell integrin expression and cytoskeleton organization. Specific Aim 2: To determine whether matrix molecule glycosylation interferes with response of cutaneous cells to substance P. We will determine whether matrix molecule glycation decrease substance P-induced NGF synthesis or changes in endothelial cell cytoskeletal organization and/or integrin expression. Specific Aim 3: To determine the effect of hyperglycemia and matrix molecule glycosylation on neutral endopeptidase expression and activity by

cutaneous cells. We will determine whether hyperglycemia or matrix molecule glycation increases neutral endopeptidase activity by cutaneous cells. We will determine whether hyperglycemia or matrix molecule glycation increases neutral endopeptidase expression and activity by microvascular endothelial cells or keratinocytes. Specific im 4: To determine whether restoration of neuropeptides or neurotrophins improves wound repair in diabetic (db/db) mice. Using an excisional would model in hyperglycemia db/db mice, we will replace substance P, replace NGF or inhibit neutral endopeptidase activity to evaluate the roles of neuropeptides and NGF in wound repair.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: EPIDERMAL INNERVATION AS AN OUTCOME MEASURE**

  Principal Investigator & Institution: Herrmann, David N.; Neurology; University of Rochester Orpa - Rc Box 270140 Rochester, Ny 14627

  Timing: Fiscal Year 2002; Project Start 15-MAY-2002; Project End 30-APR-2007

  Summary: (provided by applicant) This application describes a plan that combines recently developed clinical tests and laboratory methodologies to improve our ability to carry out therapeutic trials in small-fiber sensory neuropathies. This career development application will build upon the clinical expertise of Dr. Herrmann in neuromuscular disorders, electrophysiology, and peripheral nerve histopathology. The long-range goal of Dr. Herrmann is to develop a successful independent research program that includes both investigations of the pathomechanism of different small fiber sensory neuropathies and the performance of therapeutic trials in these disorders. To achieve these objectives the candidate will: 1) learn clinical research methodology through didactic course work, 2) study peripheral nerve biology and the neurobiology of pain through a structured reading program, 3) undertake a mentored, patient oriented research project aimed at the development of optimal outcomes measures for clinical trials in **peripheral neuropathy,** 4) develop collaborative research studies aimed at understanding the neurobiology of pain in small fiber neuropathies. The mentored research project will test the hypotheses that: 1)serial measurements of epidermal nerve fiber density (ENF) and morphology are useful as outcome measures in studies of small fiber sensory neuropathy; 2) redistribution and accumulation of novel PN3 sodium channels at sensory nerve terminals occur during the transition from asymptomatic to symptomatic HIV associated distal symmetrical polyneuropathy (DSP), and that these changes contribute to the production of neuropathic pain. This research project will be carried out in a large NIH-funded cohort at high risk for HIV-associated DSP. Through the use of serial punch skin biopsies, Dr. Herrmann will compare changes in ENF density and morphology and the level of expression of novel PN3 sodium channels at sensory nerve terminals to several clinical/laboratory measures which include: a) a patient generated pain scale; b) quantitative sensory testing; c) sural nerve conduction; and d) autonomic function. Dr. Herrmann will also examine a method to simplify the analysis of skin biopsy specimens, for easier application in large clinical trials.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: FDG-PET IMAGING IN COMPLICATED DIABETIC FOOT**

  Principal Investigator & Institution: Alavi, Abass; Professor of Radiology, Neurology and Ps; Radiology; University of Pennsylvania 3451 Walnut Street Philadelphia, Pa 19104

  Timing: Fiscal Year 2002; Project Start 30-SEP-2002; Project End 31-AUG-2006

Summary: (provided by applicant): Approximately 25 percent of the 11 million Americans with diabetes suffer from **peripheral neuropathy** and diabetic related foot complications account for the majority of nontraumatic amputations of the lower extremity. In this population, osteomyelitis and deep infection of the foot are relatively common complications. Early diagnosis of these complications is crucial in the management of these patients, because prompt antibiotic treatment cure infection and therefore can decrease the rate of amputation. However, establishing the diagnosis of osteomyelitis is quite difficult in this setting because of concurrent conditions, such as peripheral vascular disease, cellulitis, neuropathy and osteoarthropathy, which can obscure the clinical manifestations of osteomyelitis. Much of the amputations are due to the lack of a single test that is highly sensitive, specific and cost effective in the early diagnosis of osteomyelitis. Current diagnostic tests including routine radiography, laboratory studies, nuclear medicine procedures, and magnetic resonance imaging (MRI) suffer from significant shortcomings such as inadequate accuracy and cost. It has been shown that [18F] fluorine deoxyglucose (FDG) and Positron Emission Tomography (PET) reveal sites of inflammation with high sensitivity and accuracy. In the pilot study conducted at our institution, we have been able to demonstrate that FDG-PET imaging has high accuracy in the diagnosis of orthopedic infection in a small patient population. The main objective of the proposed research study is to determine the efficacy of FDG-PET imaging in the diagnosis of osteomyelitis or deep infection in patients with diabetic foot in a large patient population. We also intend to compare FDG-PET imaging directly to MRI to determine whether FDG-PET imaging is superior to this commonly used technique. We will also examine the potential utility of a novel magnetic resonance (MR) technique (developed by one of our investigators) in detecting marrow edema and bone loss as a result of such complications. We plan to enroll 240 patients over four years for the purposes outlined in the application. By utilization of the proposed work, we will be able to demonstrate the sensitivity, specificity, and effectiveness of this technique in the management of patients with diabetic foot. We believe this promising technology has great potential for the accurate diagnosis of this serious and challenging clinical problem, and may substantially influence the outcome in these patients.

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- **Project Title: FUNCTION AND REGULATION OF INTERCELLULAR COMMUNICATION**

  Principal Investigator & Institution: Paul, David L.; Professor; Neurobiology; Harvard University (Medical School) Medical School Campus Boston, Ma 02115

  Timing: Fiscal Year 2003; Project Start 01-DEC-1986; Project End 30-JUN-2007

  Summary: (provided by applicant): Previously, we showed that mutations in the gene encoding connexin32 (Cx32) caused a demyelinating **peripheral neuropathy** called Charcot-Marie-Tooth disease (CMTX). Consistent with this finding, Schwann cells contain Cx32 and regulate its expression like a myelin-related gene. Thus, maintenance of myelin in the human peripheral nervous system requires connexin expression. However, oligodendrocytes also express and regulate Cx32 like a myelin gene and yet central abnormalities are rare in CMTX patients. Since one explanation for this discrepancy would be redundant expression of other connexins, we searched for connexins in myelinating glia. We found two novel connexins, Cx29 and Cx47. All three connexins can be found in oligodendrocytes and Schwann cells. Cx29 and Cx32, however, are present in non-overlapping subsets of spinal cord oligodendrocytes and,while they are both present in Schwann cells, their subcellular distributions are strikingly different. Single knockouts of either Cx32 or Cx47 myelinate relatively

normally and have no functional deficits. In contrast, double knockouts develop severe central demyelination and die during the 6th postnatal week of life. Surprisingly, these animals display only subtle abnormalities in peripheral myelin. Together, our studies suggest that connexins are critical for both central and peripheral myelination but that different connexins may have different functions within myelinating glia. We propose to define the separate and interacting roles of connexins in myelination using a combination of immunocytochemistry, targeted gene ablation and functional analysis of connexin channel activity.

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- **Project Title: GAP JUNCTIONS AND SCHWANN CELLS**

  Principal Investigator & Institution: Spray, David C.; Professor; Neuroscience; Yeshiva University 500 W 185Th St New York, Ny 10033

  Timing: Fiscal Year 2001; Project Start 05-FEB-1996; Project End 31-MAR-2003

  Summary: The overall goal of these studies is to define the role that gap junctions play in the functions of myelinating, non-myelinating and proliferating Schwann cells in the peripheral nervous system. Because point mutations in Cx32 are responsible for the X-linked form of Charcot-Marie-Tooth syndrome (CMTX), a demyelinating **peripheral neuropathy,** we are particularly interested in correlated changes in Cx32 expression with myelination in vivo and in culture and in properties of CMTX mutant channels. Because expression of other gap junction proteins (connexins) can be induced in myelinating Schwann cells by nerve injury, we are also interested in the nature of this induction and the changes in Schwann cell behavior when different connexin are expressed. We will apply a broadly based approach to the studies, taking advantage of recently developed animal models deficient in myelin proteins and making use of transfection technology in Schwann cells and cell lines. Specific Aim 1. To compare the functional properties of Schwann cells cultured from myelinated and nonmyelinated nerves of wildtype mice and transgenic mice in which connexin expression is altered. Specific Aim 2. To determine turnover dynamics and transport characteristics of the connexins and their mRNAs that are expressed in myelinating, nonmyelinating and proliferating Schwann cells in wildtype and connexin-altered transgenic mice. Specific Aim 3. To determine the impact of myelin-related genes on gap junction properties using transfected cell lines and Schwann cells cultured from transgenic mice in which myelin-related proteins are altered. Together, these studies should answer major questions regarding basic biology of Schwann cells and the role of gap junctions in physiological and pathophysiological conditions.

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- **Project Title: GENETICS AND EPIDEMIOLOGY OF ESSENTIAL TREMOR**

  Principal Investigator & Institution: Gilbert, John R.; Associate Research Professor; Medicine; Duke University Durham, Nc 27706

  Timing: Fiscal Year 2002; Project Start 15-MAR-2002; Project End 28-FEB-2006

  Summary: Essential Tremor (ET) is a heterogenous tremor disorder characterized by a core group of features. The tremor syndrome is characterized by postural and kinetic tremor affecting the arms and hands, although the head, voice, and legs may also be affected. Although frequently described as a benign disorder, this is not true; many patients are socially and physically handicapped, with some patients being totally disabled. The differential diagnosis list for ET is extensive including dystonia, Parkinsonism, myoclonus, **peripheral neuropathy,** and other conditions. Prevalence

estimates range widely, depending upon methodology and diagnostic criteria, from 0.003 to as high as 2% in the general population, with as much as 5% of the population affected over the age of 65. There are no known biological or diagnostic neuropathological markers for ET. The estimates of ET cases presenting with a positive family history range from 17.4% to 100%. Recent studies indicate that up to 96% of ET may be dominantly inherited. Clinical and genetic heterogeneity have slowed linkage studies. To date three loci associated with ET have been linked: 1) Familial Essential Tremor 1 (FET1) has been mapped in a series of Icelandic families on chromosome 3q13; (2) ETM mapped, in four unrelated US families, to chromosome 2p22-p25; and (3) a third locus maps, in a family that segregates both Parkinson's disease and postural tremor consistent with ET, to Chromosome 4p. We have, to date, ascertained, twelve ET and ET/PD linkage quality families. The largest pure ET kindred (DUK13001) have been excluded from known ET loci. The aims of this proposal are to ascertain and sample large families with ET, carry out a complete ET genome scan to establish linkage for these and additional ET families, identify new ET disease loci, and isolate and characterize ET genes, beginning with DUK13001 ET family.

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- **Project Title: GENETICS OF JUVENILE AMYOTROPHIC LATERAL SCLEROSIS (JALS)**

  Principal Investigator & Institution: Chance, Phillip F.; Professor; University of Pennsylvania 3451 Walnut Street Philadelphia, Pa 19104

  Timing: Fiscal Year 2001

  Summary: Chronic Juvenile Amyotrophic Lateral Sclerosis (JALS) combines the features of a spinal muscular atrophy syndrome with upper motor neuron dysfunction. We have identified a large pedigree in Southern Maryland segregating an autosomal dominant gene for this form of JALS. Over 75 persons in this family are affected with a **peripheral neuropathy** characterized by an age of onset in adolescence with slow progression, leading to severe neuromuscular impairment by the fourth and fifth decades. Altered or abnormal expression of a motor neuron-specific component or a more widely-expressed protein whose function is crucial to motor neuron function is suspected. The gene for this disorder does not map to known regions of other motor neuron syndromes including the Familial Amyotrophic Lateral Sclerosis (ALS1) locus on chromosome 21, the Juvenile Amyotrophic Lateral Sclerosis (ALS2) locus on chromosome 2 or to the Spinal Muscle Atrophy (SMA) locus on chromosome 5. We propose to investigate the molecular basis of the JALS gene in this pedigree by techniques of positional cloning, including linkage analysis, physical map construction and analysis of transcripts and candidate genes. Experiments aimed to characterize the patterns and distribution of expression of this gene at the transcriptional and protein revels are proposed through in situ hybridization analysis, construction of transgenic animals, protein/antibody production and analysis in a motor neuron cell culture system. Genetic analysis in this large JALS pedigree affords the opportunity to identify and characterize an important motor neuron component.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: GLYCOLIPIDS AND EXPERIMENTAL NEUROPATHY**

  Principal Investigator & Institution: Yu, Robert K.; Director, Institute of Molecular; Biochem and Molecular Biology; Medical College of Georgia 1120 15Th St Augusta, Ga 30912

Timing: Fiscal Year 2003; Project Start 01-JUN-1988; Project End 30-NOV-2006

Summary: (provided by applicant): The long-term goal of this project is to better understand the pathogenic role of anti-carbohydrate antibodies in **peripheral neuropathies** and related neurological disorders and to develop rational and effective therapeutic strategies to these debilitating diseases. Previous studies have demonstrated that in patients with **peripheral neuropathy** and paraproteinemia, glycolipid/glycoprotein antigens that bear the epitope HNK-1 (CD57 or SGA) are involved. The structures of the glycolipid antigens were characterized in our laboratory as sulfoglucuronosyl glycolipids (SGGLs). Antibodies against SGGLs are involved in the pathogenesis of immune-mediated **peripheral neuropathies** because: a). the antigens are localized in PNS myelin and axolemma; the degeneration of which accounts for the loss of sensory and motor functions; b). animal models of **peripheral neuropathies** can be established using pure glycolipid antigens; c). an antibody-mediated, complement-dependent demyelinating and axonal degenerating process has been established in animals models; d). the presence of SGGLs in endothelial cells (ECs) provides a mechanism that accounts for an antibody-mediated breakdown of the blood-nerve barrier (BNB); and e). the upregulation of the expression of SGGLs is effected by treatment of the ECs by inflammatory cytokines, such as IL-1beta, resulting in greater attachment of leucocytes to the EC surface. Emerging evidence has indicated that other anti-carbohydrate antibodies may be involved in similar neurological disorders, such as anti- GM1 in Guillain-Barre syndrome. Since most of these disorders have antecedent infections, we propose a unified hypothesis (molecular mimicry) regarding anti-carbohydrate antigens by examining the nature of other potential glycoconjugate antigens, particularly bacterial lipopolysaccharides, that share common carbohydrate epitopes in nerve. We will examine the origin of the anti-carbohydrate antibodies and the involvement of these glycoconjuates in eliciting autoimmune responses in animal and man. Since abrogation of the BBB and BNB is a prerequisite of immune-mediated neurological disorders, we will examine the biological function of ECs in the maintenance of BBB and BNB function in normal and pathological conditions. We will develop a new class of anti-inflammatory agents using antisense techniques to suppress the expression of glycoconjugate adhesion molecules to prevent inflammatory T cells and circulating antibodies from attachment to the vascular bed. We will also devise peptide mimics of anti-carbohydrate antibodies by phage display techniques for the treatment for anti-carbohydrate antibody-induced neuropathies and related neurological disorder.

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- **Project Title: HEARING DEFICIT DUE TO AUDITORY NEUROPATHY**

  Principal Investigator & Institution: Starr, Arnold; Professor; Neurology; University of California Irvine Irvine, Ca 926977600

  Timing: Fiscal Year 2002; Project Start 01-SEP-1996; Project End 28-FEB-2005

  Summary: (provided by applicant): This proposal will study a recently recognized form of hearing disorder called auditory neuropathy (AN). Different from cochlear damage, AN is characterized by normal measures of cochlear outer hair cells but abnormal measures of the central auditory pathway beginning with auditory nerve. The hearing disorder typically affects speech comprehension out-of-proportion to the pure tone loss, particularly speech recognition in noise. AN is not rare and accounts for 10 percent of newborns identified as having hearing loss. The disorder occurs in children and adults. In adults the disorder is commonly associated with a **peripheral neuropathy.** Loss of neural synchrony is proposed as a cardinal mechanism underlying the hearing disorder.

The sites of abnormality in AN could include auditory nerve and/or inner hair cells and their synapses with auditory nerve dendrites. Our long-term goals are to understand the AN mechanisms and functions in order to provide a scientific basis for alleviating the hearing deficit in AN subjects. We propose three experiments using both psychophysical and elecrophysiological techniques to characterize: (1) fundamental and complex auditory processes in AN subjects in order to explain their speech recognition difficulty, particularly in noise; (2) distinguish between the site of the disorder as being at auditory nerve or at inner hair cell/synapse complex; and (3) optimize signal processing for AN subjects with cochlear implants. The resultsof our studies could have major impact on the diagnosis, classification, and treatment of auditory neuropathy.

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- **Project Title: IGF-I PROTECTS NEURONS FROM GLUCOSE INDUCED CELL DEATH**

  Principal Investigator & Institution: Russell, James W.; Professor; Neurology; University of Michigan at Ann Arbor 3003 South State, Room 1040 Ann Arbor, Mi 481091274

  Timing: Fiscal Year 2001; Project Start 01-DEC-1996; Project End 30-NOV-2001

  Summary: Diabetic neuropathy (DN) is the most common cause of **peripheral neuropathy** in the United States, yet the pathogenesis remains unknown. Although diabetes can affect all peripheral neurons, sensory neurons are most commonly affected, possibly because dorsal root ganglion (DRG) neurons reside outside the blood-nerve barrier. Hyperglycemia has been implicated in both animal and human studies in the pathogenesis of DN and recent clinical trials have shown a reduction in the progression of DN with careful control of blood glucose an intensive insulin therapy. However even excellent glycemic control fails to prevent or reverse DN. Insulin-alike growth factor I (IGF-I) can improve glycemic control in diabetes and is able to promote neuronal growth, development, and regeneration of neurons. In ongoing preliminary studies, we find that hyperglycemia leads to impaired rat DRG sensory neuronal growth and programmed cell death (PCD). In both paradigms, IGF-I is neuroprotective. Our initial investigations of IGF-I neuroprotection reveal that 1) IGF-I acts trough the type I IGF receptor (IGF-IR activation results in downstream phosphorylation of focal adhesion proteins involved in organization of the actin cytoskeleton and neurite formative, and 3) IGF-IR activation of phosphatidylinositol-3 kinase (PI-3K) is essential for rescue of neuronal cells from PCD. We have developed a novel hypothesis to explain hyperglycemic coupled neurotoxicity. We speculate that high glucose alters IGF-IR activation in DRG neurons. This result in changes in the phosphorylation of focal adhesion proteins which results in disruption of the actin cytoskeleton and impairs DGR neurite growth. We believe subsequent cytoskeletal changes alone, or in conjunction with direct glucose toxicity, induce PCD in DRG neurons. Activation of IGF-IR 1) prevents PCD by enhancing focal adhesion protein phosphorylation and stabilizing the cytoskeleton, and/or 2) blocks PCD by activating PI 3K pathways, which may effect PCD regulatory proteins like bcl-2 and/or death proteases. In this proposal we will test each component of the model. We have 2 aims: 1. Examine the effect of high glucose on DRG neurons. In DRG neurons, in response to high glucose, examine: a) DRG neuronal morphology and neurite growth b) IGF-IR transcription, cell surface abundance, and autophosphorylation c) Phosphorylation of focal adhesion proteins and the DRG cytoskeleton and d) PCD in DRG 2. Characterize IGF-IR protection of DRG neurons following glucose exposure. In DRG neuron, in response to high glucose, examine the effect of IGR-I on: a) DRG neuronal morphology and neurite growth b) IGF-IR transcription, cell surface abundance, and autophosphorylation c) Phosphorylation of

focal adhesion proteins and the DRG cytoskeleton 3. Investigate the components underlying IGF-IR rescue of DRG from glucose-induced PCD. a) Determine the association between the observed changes in focal adhesion proteins, the cytoskeleton, an PCD pathways in response to high glucose b) Examine the effect of high glucose and IGF-I on IGF-IR activation of PI-3K c) Ascertain if IGF-IR activation prevents PCD by promoting expression of regulatory proteins that suppress cell death, like bcl-2 d) Determine if high glucose promotes PCD by activation of death proteases, and the role of IGF-IR activation in modulating this PCD pathway. IGF-I is currently undergoing evaluation in clinical trails of diabetic neuropathy. The current proposal will help elucidate the mechanisms underlying the role of IGF-I in preventing changes in neuronal morphology and PCD in diabetic neuropathy.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: IMMUNOPHILIN LIGANDS FOR HIV DEMENTIA AND NEUROPATHY**

  Principal Investigator & Institution: Nath, Avindra; Professor; Neurology and Neurosurgery; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2003; Project Start 08-SEP-2003; Project End 30-JUN-2007

  Summary: As patients are living longer with HIV infection, neurological complications such as dementia and **peripheral neuropathy** are becoming more prevalent and an important cause of morbidity in this population. To date, however, there is no effective treatment for these complications. Both the brain and the dorsal root ganglia show evidence of neurodegeneration while the virus replicates in glial cells or infiltrating monocytes. This suggests an important role for neuroprotective and neurotrophic modes of treatment for these conditions. This program project grant brings together researchers from several disciplines to closely interact with one another to develop new modes of treatment. During the duration of this program project we propose to conduct basic mechanistic in vitro studies using unique in vitro models for HIV dementia and **peripheral neuropathy** and to conduct animal studies as well as a phase 2 clinical trial. These projects will closely interact with a pharmaceutical company that has developed some novel immunophilin ligands that are highly potent neuroprotective and neurotrophic agents. We have taken a bench to bedside approach to evaluate their clinical use. A unique strength of this proposal is that it will identify compounds that are useful for treating both HIV dementia and **peripheral neuropathy,** since these conditions may coexist and occasionally may be difficult to differentiate. We have proposed five interactive projects and one core. Project l will determine the use of these agents in a human in vitro model for HIV dementia, Project 2 will similarly study the agents in the context of dorsal root ganglia neurons, Project 3 will determine subcellular mechanisms involved in neuroprotection. Project 4 will determine the use of a select compound in an SIV model of HIV dementia and **peripheral neuropathy.** Project 5 will conduct a phase 2 clinical trial of the compound identified as the lead candidate from the above projects. During the initial years of the Program project animal and clinical projects will develop and validate some novel tests that would serve as critical outcome measures during the trial. An administrative core will coordinate the interactions between all the projects and each of the researchers.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: IMPAIRED GLUCOSE TOLERANCE CAUSES NEUROPATHY**

  Principal Investigator & Institution: Singleton, John R.; Associate Professor; Neurology; University of Utah 200 S University St Salt Lake City, Ut 84112

Timing: Fiscal Year 2002; Project Start 20-AUG-2002; Project End 31-JUL-2005

Summary: (provided by the applicant): Sensory neuropathy, often with pain, is a common neurologic patient. In developed countries, type-2 diabetes is the most frequently-defined cause of sensory neuropathy. We have found that 36 of 72 prospectively evaluated patients with otherwise idiopathic **peripheral neuropathy** have Impaired Glucose Tolerance (IGT). This is a significantly greater frequency of IGT (50%) than reported in large epidemiological studies of the age-matched general population (14%). IGT, defined as a 2-hour Oral Glucose Tolerance Test (OGTT) between 140 and 200 mg/dl, represents an intermediate defect in glucose metabolism, which correlates with insulin resistance syndrome, and has been shown to carry an independent risk for cardiovascular morbidity. Patients with IGT almost uniformly have a painful sensory neuropathy, linking them to the phenotype of early diabetic neuropathy. The recently completed Diabetes Prevention Program (DPP) shows that intensive diet and exercise modification can slow progression from IGT to diabetes. The Diabetes Control and Complications Trial (DCCT) clearly shows that neuropathy onset and severity correlates with glycemic control in diabetes. In the DCCT, aggressive treatment of hyperglycemia prevented or slowed the progression of neuropathy. We hypothesize that the post-prandial hyperglycemia, identified by IGT, causes or contributes to a painful, small fiber neuropathy, which is indistinguishable from that observed in early frank diabetes, and that aggressive treatment to normalize hyperglycemia will slow or prevent progression of neuropathy. The purpose of this Clinical Pilot Study is to lay the groundwork for a prospective clinical trial in patients with IGT, and neuropathy, to determine if intensive exercise and diet counseling alone, or with a glucose-lowering agent, can stabilize or reverse neuropathy. We have three specific aims:1. Confirm the statistical association between IGT and neuropathy using control subjects with chronic pain, matched for age and body mass index.2. Characterize the clinical, electrodiagnostic, and histologic phenotype of neuropathy associated with IGT.Define the progression of neuropathy associated with IGT using two validated measures of neuropathy severity (cold detectiort threshold and nerve conduction velocity), and validate the use of intraepidermal nerve fiber countin as a measure of small fiber neuropath progression.

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- **Project Title: LAMICTAL IN ADULTS WITH HIV PERIPHERAL NEUROPATHY**

  Principal Investigator & Institution: Schiffito, Giovanni; University of Rochester Orpa - Rc Box 270140 Rochester, Ny 14627

  Timing: Fiscal Year 2002

  Summary: This abstract is not available.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: LAMININ ALPHA 2 IN TISSUE REGENERATION**

  Principal Investigator & Institution: Engvall, Eva S.; Associate Scientific Director; Burnham Institute 10901 N Torrey Pines Rd San Diego, Ca 92037

  Timing: Fiscal Year 2001; Project Start 01-MAR-1996; Project End 28-FEB-2005

  Summary: (Adapted from applicant's abstract) Tissue regeneration and repair are critical to longevity. Insufficient regeneration of muscle and nerve is a significant cause of morbidity in patients with muscular dystrophy and other muscle and nerve diseases and in the aging individual. The laminin subunit a2 is prominently expressed in striated muscle and peripheral nerve, and mutations in the lama2 gene cause a severe form of muscular dystrophy in humans (merosin-deficient congenital muscular dystrophy,

MCMD) and mice. A mouse model for human MCMD was generated by disrupting the lama2 gene with the lacZ reporter gene. Homozygous mutant mice develop muscular dystrophy and **peripheral neuropathy** after birth. Absence of laminin a2 does not significantly affect myogenesis, but the differentiated laminin a2-deficient muscle are highly susceptible to injury upon contraction. Most important, in contrast to the apparent normal development, regeneration is severely compromised in the absence of laminin a2. It is proposed to use in vivo and in vitro models to analyze development and regeneration of skeletal muscle and peripheral nerve to determine which steps in the regeneration process are dependent on laminin a2. The regeneration-promoting effects of laminin a2 will be analyzed in transgenic mice with tissue-specific overexpression of a human LAMA2 transgene. To analyze the molecular pathways responsible for maturation and survival of skeletal muscle and Schwann cells, integrin and dystroglycan signaling pathways will be characterized by using the yeast 2-hybrid screening and affinity chromatography in combination with peptide mass mapping. The proposed research will result in new knowledge regarding important molecular mechanisms of muscle and nerve function and may help in devising new strategies for treatment of degenerative diseases of muscle and nerve based on promoting regeneration.

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- **Project Title: LENTIVIRUS-INDUCED NEUROPATHY: VIRAL DIVERSITY AND HOST***

  Principal Investigator & Institution: Power, Christopher T.; Associate Professor; University of Calgary 2500 University Dr Nw Calgary,

  Timing: Fiscal Year 2002; Project Start 30-SEP-2002; Project End 30-JUN-2005

  Summary: (provided by applicant): The principal neurological complication of HIV/AIDS observed in the developed world is currently **peripheral neuropathy,** usually manifested as distal polyneuropathy (DSP) or antiretroviral toxic neuropathy (ATN). This proposal examines the role of lentivirus molecular diversity in relation to the development of DSP, using multiple infectious biological strains and recombinant viruses of feline immunodeficiency virus (FIV). Based on our preliminary studies and earlier reports, we hypothesize that infection of peripheral nerves by select FIV strains, expressing different env sequence contributes to the development of DSP due to immune activation within the nerve together with concomitant systemic immune suppression. Moreover, viral heterogeneity and load within the nerve determine the severity of DSP, which can be abrogated or exacerbated with specific antiretroviral drugs. To investigate the mechanisms by which viral diversity contributes to DSP, we propose to use a well defined in vivo model of lentivirus infection in which animals infected with different strains or molecular clones of FIV are assessed neurobehaviorally, electrophysiologically, morphologically and immunologically in conjunction with analyses of viral heterogeneity and load in peripheral nerve and other organs. To support these in vivo studies, we will also explore the role of FIV env-mediated neurotoxicity using a dorsal root ganglia-derived culture system, allowing us to dissect the relative contributions of individual cell types to the pathogenesis of DSP including macrophages and Schwann cells. From these studies, we expect to gain insights into this common neurological complication in terms of lentivirus-induced neurovirulence and pathogenic host responses.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: LIPOPROTEIN LIPASE, NUTRITION AND NERVE MYELINATION**

  Principal Investigator & Institution: Eckel, Robert H.; Professor of Medicine,; Medicine; University of Colorado Hlth Sciences Ctr P.O. Box 6508, Grants and Contracts Aurora, Co 800450508

  Timing: Fiscal Year 2001; Project Start 01-JAN-1990; Project End 30-NOV-2002

  Summary: Lipoprotein lipase (LPL) is a hydrolytic enzyme which releases fatty acids and monoacylglyerol from nutrient-dependent triglyceride-rich lipoproteins [chylomicrons and very low density lipoproteins (VLDL)] and regulates the partitioning of these lipid fuels to tissues. This process has been studied most extensively in adipose tissue and muscle. However, LPL is also made in other sites including the nervous system, where the lipase is found in the brain, spinal cord and peripheral nerve. In the peripheral nerve, in vitro experiments have suggested, but not yet proven, that function of LPL is to enhance the uptake of chylomicron and VLDL triglyceride fatty acids to Schwann cells for myelin phospholipid synthesis. The studies outlined in this proposal will further this understanding by: 1) determining the sites of LPL expression within the peripheral nerve and defining the role of LPL in myelin synthesis nd peripheral nerve regeneration; 2) assessing the expression and regulation of peripheral nerve LPL in animal models of diabetic **peripheral neuropathy;** and 3) evaluating the efficacy of retro- and adenovirally mediated human LPL (hLPL) gene delivery to augment myelination following peripheral nerve injury, and reverse and/or retard the neuropathy of diabetes mellitus. A combination of experiments in rodents and cultured Schwann cells will be utilized. To more specifically determine the role of the LPL in peripheral nerve in rodents (Specific Aim #1), the cells of origin and response of LPL to crush injury will be examined in normal rats and mice, and in transgenic mice without LPL in the peripheral nerve. In Specific Aim #2, several models of diabetic mellitus with already characterize **peripheral neuropathy** will determine if LPL expression in the peripheral nerve injury is impaired +/- crush injury. Finally, in Specific Aim #3, an important series of experiments will determine the efficacy of the delivery of LPL to augment myelination in regenerating nerves and in rodents with diabetic **peripheral neuropathy.** Two viral gene delivery systems will be evaluated for their ability to deliver hLPL to rat sciatic nerve: retrovirus-mediated gene delivery, which targets dividing cells, and adenovirus-mediated gene delivery, which introduces genes into non-dividing cells. The method that better facilitates sciatic nerve recovery from crush injury will then be administered to rodent models of diabetic neuropathy in an attempt to improve peripheral nerve myelination. Overall, these studies should provide a comprehensive understanding of the role of LPL in the peripheral nerve. Moreover, we are hopeful that new insights into the treatment of **peripheral neuropathies** will also ensue.

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- **Project Title: MECHANISMS OF ACTION OF HIGHLY EFFICACIOUS PGA-TAXOL**

  Principal Investigator & Institution: Li, Chun; Associate Professor; Diagnostic Radiology; University of Texas Md Anderson Can Ctr Cancer Center Houston, Tx 77030

  Timing: Fiscal Year 2001; Project Start 15-JUL-1997; Project End 30-JUN-2002

  Summary: Taxol (paclitaxel) has shown significant activity against several types of malignant diseases, including breast cancer. As with most chemotherapeutic agents, however, the maximal dose of taxol is limited by toxicity. In humans, drug-induced toxicity is manifest as granulocytopenia and **peripheral neuropathy.** Other major difficulties in the clinical use of taxol include poor aqueous solubility and drug

resistance. A strategy of polymer-drug conjugation has been attempted to improve the utility and efficacy of taxol. Specifically, a highly water-soluble polymer-taxol conjugate (PGA-taxol) which has shown remarkable in vivo antitumor activity in two rodent tumor models has been developed. In rats bearing intramuscularly implanted 13762 mammary tumor (approx. 2400 mm3 at time of treatment), a single intravenous injection of PGA-taxol at a dose of 40 mg equiv. Taxol/kg body weight induced complete tumor regression. In comparison, the same dose of taxol delayed tumor growth only 9 days (vs. Cremophor vehicle-treated controls). Furthermore, the inhibition of tumor growth by PGA-taxol was achieved with less toxicity than that produced by the less effective taxol treatment. Additionally, PGA-taxol showed activity against taxol-resistant tumor cells, demonstrating that conjugation of chemotherapeutic drugs to polymeric carries may be an useful strategy to overcome drug resistance. To better understand the enhanced antitumor efficacy of PGA-taxol and aid in the future design and development of polymeric drug carriers for selective delivery of chemotherapeutic agents, it is important to investigate further the pharmacological and toxicological properties of PGA-taxol. These studies should also be crucial in planning future human trials of PGA-taxol as a potentially powerful anti-cancer agent. The specific aims of this proposal are (1) to synthesize and characterize monomeric glutamic acid-taxol conjugate and PGA- taxol conjugates of different molecular weights; (2) to study their in vitro cytotoxicity and cellular accumulation kinetics; (3) to examine whether PGA-taxol has a unique mechanism of action different from that of taxol; (4) to assess their toxicity and in vivo antitumor activity in appropriate tumor models; and (5) to study their pharmacokinetics, tissue distribution, and intratumoral distribution.

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- **Project Title: MECHANISMS OF AXONAL DEGENERATION**

  Principal Investigator & Institution: Glass, Jonathan D.; Professor; Emory University 1784 North Decatur Road Atlanta, Ga 30322

  Timing: Fiscal Year 2001

  Summary: Axonal degeneration, or death of nerve fibers, is the most common pathological finding in the majority of neurological disorders, including stroke, head and spinal cord trauma, and **peripheral neuropathy.** There is a paucity of data regarding the basic mechanisms of axonal degeneration, and it is unclear whether axonal death in each of these disorders occurs via multiple or common pathways. Experimental studies, however, support the idea that calcium entry and protease activation are important. The long term goal of these studies is to understand the basic mechanisms leading to axonal degeneration using clinically relevant models of disease, and to use these new data to direct strategies for prevention of axonal degeneration and thus preservation of neurological function. The experimental design exploits: 1) the sensory ganglia culture system for manipulating rodent axons in a reproducible in vitro setting, and 2) the WLD mouse, a unique mutant strain whose sole phenotype is resistance to traumatic axonal degeneration. Aim 1 will test the hypothesis that axonal death caused by trauma (axotomy) and exposure to a neurotoxin (vincristine) occurs by a common mechanism involving calcium entry and activation of the protease, calpain. In Aim 2, axons from the WLD mouse which are resistant to axotomy-induced degeneration will be used to further test the hypothesis stated in Aim 1. These axons will be tested for their ability to resist degeneration when exposed to a neurotoxin induced axonal degeneration. Aim 3 will ask when calcium entry and calpain activation occur after nerve injury, and what relationship these events have to axonal degeneration. Aim 3 will ask when calcium entry and calpain activation occur after

nerve injury, and what relationship these events have to axonal degeneration. Using state-of-the-art imaging techniques, the proximal and distal portions of transected nerve fibers will be compared since they are exposed to the same injury, but one survives and the other dies. Aim 4 is directed at identifying proteases other than calpain that are present and active in degenerating nerve fibers, with the premise that a directed strategy for preventing axonal degeneration during disease requires an intimate understanding of all of the processes involved. Overall, the achievement of these Aims will provide a new appreciation of the mechanisms of axonal degeneration that will certainly impact on treatment strategies for a number of brain, spinal cord, and peripheral nerve diseases.

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- **Project Title: MECHANISMS OF NEUROPROTECTION OF IMMUNOPHILIN LIGANDS**

  Principal Investigator & Institution: Steiner, Joseph P.; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2003; Project Start 01-APR-2003; Project End 31-MAR-2007

  Summary: Neuroimmunophilln ligands are orally active small molecules which protect neuronal cells and can stimulate morphologic and functional recovery of injured axons in vitro and in vivo. Neurotrophic actions of these ligands have been demonstrated in neurons and axons in the central and peripheral nervous systems. These ligands are currently being evaluated in human clinical trials as treatments and therapies for neurodegenerative disorders, such as Parkinson's Disease. Another clinical trial utilizing GPI 1485 as a neuroprotective molecule to spare peripheral axons and maintain erectile function following bilateral nerve sparing prostatectomy is scheduled to begin in early 2003. Treatment of vulnerable peripheral neurons with these compounds may provide significant benefit to patients with painful **peripheral neuropathy** resulting from HIV infection and the ensuing treatment. However, the neurotrophic mechanism of action of this class of compounds is not well understood. In these studies, we propose to address the question of mechanism by identifying downstream binding targets of the GPI 1485-FKBP complex in neurons. We propose to use affinity chromatography and biochemical techniques to determine direct binding proteins of GPI 1485. We will complement these studies by evaluating mRNA and protein expression profiles in neuropathologic states following drug treatment. In addition, we will also evaluate the different biologic pathways utilized by neurotrophic FKBP and cyclophilin ligands. Cyclophilin ligands may act as neuroprotective molecules by interacting with cyclophilin D on the mitochondrial membrane. Therefore, we will also determine the protective role of cyclophilin ligands in mitochondrial dysfunction.

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- **Project Title: METABOLISM OF SHORT CHAIN ACYL-COA'S AND ITS DEFICIENCY**

  Principal Investigator & Institution: Vockley, Gerard; Professor and Chair; Mayo Clinic Rochester 200 1St St Sw Rochester, Mn 55905

  Timing: Fiscal Year 2003; Project Start 15-FEB-1999; Project End 28-FEB-2007

  Summary: (provided by applicant): The acyl-CoA dehydrogenases (ACDs) are a family of highly conserved enzymes which catalyze the first intra-mitochondrial step in fatty acid beta-oxidation and branched chain amino acid metabolism. Deficiencies of these enzymes represent a cause of considerable morbidity and mortality in both children and

adults and can present with episodic metabolic decompensation, mental retardation, myopathy, cardiomyopathy, hypoglycemia and **peripheral neuropathy.** Abnormalities of the short chain acyl-CoA dehydrogenase (SCAD) have proven particularly difficult to diagnose and study. Two common variants of SCAD have been identified, however, their role in causing disease is unclear. In the first funding period of this grant, we have shown that the two common polymorphic variants are functionally impaired, suggesting a possible pathophysiologic role in these individuals. We have also identified a new ACD [isobutyryl-CoA dehydrogenase (IBD)] active in the valine catabolic pathway, as well as the first patients deficient in IBD and short/branched chain ACD (SBCAD). The long range goal of the project continues to be characterization of the metabolism of short chain acyl-CoAs in humans, and deficiency of these enzymes at the biochemical, structural and molecular level. Specific aims of this renewal application include: Specific Aim 1, to identify molecular defects responsible for causing SBCAD, and IBD deficiencies, and to characterize the effects of mutations on enzyme function. Specific Aim la is to identify mutations in the SBCAD and IBD genes in patients with deficiencies of these enzymes. Specific Aim lb is to demonstrate the biological importance of SBCAD and IBD mutations using a variety of in vivo and in vitro expression techniques. Specific Aim lc is to further characterize genotype/phenotype relationships in these disorders. Specific Aim 2 is to characterize the structural motifs important in determining substrate specificity in the branched chain ACDs. Specific Aim 2a is to characterize substrate binding to rat and human SBCAD using surface plasmon resonance techniques. Specific Aim 2b is to determine the amino acid residues and motifs important in determining the specificity of SBCAD and IBD towards short and short branch chain acyl-CoA substrates. Specific Aim 2c is to determine the crystal structure of SBCAD and IBD. This will be performed by my collaborator Dr. Jung-Ja Kim. Specific Aim 3 is the determination of amino acid residues and motifs important for stabilization of ACD homotetramers. Aim 3a is to make mutant human IVDs based on the potato enzyme that will be stable, active dimers. Aim 3b is to identify residues in human IVD that are important in determining tetramer stability.

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- **Project Title: MIAMI ADULT AIDS CLINICAL TRIALS GROUP, AACTG**

  Principal Investigator & Institution: Fischl, Margaret A.; Associate Professor; Medicine; University of Miami-Medical Box 248293 Coral Gables, Fl 33124

  Timing: Fiscal Year 2001; Project Start 01-APR-1992; Project End 31-DEC-2004

  Summary: (adapted from application's abstract): The Miami ACTU has been a member of the AACTG since its inception and has contributed to a number of AACTG studies that led to the approval of seven antiretroviral drugs and numerous HIV treatment strategies including lower and alternative dosing schedules for all three classes of antiretroviral agents, early treatment intervention, combination therapies with dual NRTIs and triple-drug therapy. The Miami ACTU has also actively participated in the Virology Laboratory Subcommittee working groups with an active role in the standardization of a PBMC culture assay for determining drug susceptibility, the assessment of interlaboratory concordance of DNA sequencing analysis of HIV RT, and the development of a consensus sequencing protocol to detect drug resistant mutations. This unit has also been involved with the Surrogate Markers Subcommittee with an active role in the assessment of plasma cytokines and soluble markers, cytotoxic T-lymphocyte activity, lymphocyte proliferation and advanced flow cytometry, and defining and validating immunologic markers as surrogate markers independent of CD4 and HIV RNA. Finally, this unit has contributed to the Pharmacology Committee

with the evaluation of targeted- concentration control studies and the correlation of drug exposure with treatment response and failure parameters. The Miami ACTU will actively participate in HIV Disease RAC efforts and provide expertise to address study treatment strategies for initial therapy, treatment options for virologic failure and utilization of phenotypic and genotypic assessments to direct subsequent therapy and treatment intensification. The Miami ACTU will also bring expertise in the areas of hepatitis B and C pathogenesis and treatment, metabolic complications of HIV-1 protease inhibitor pathogenesis and treatment, HIV dementia pathogenesis and treatment and **peripheral neuropathy** pain assessment, Kaposi sarcoma (KS) pathogenesis, intensive immunologic monitoring and definition, and validation of immunologic determinants of treatment response. The Miami ACTU plans to enroll 100 subjects per year across AACTG studies and 70 patients into AACTG substudies, including but limited to Compartmental, Virology, Viral Dynamics, Pharmaceuticals, Metabolic, Neurologic, Women's Health and Adherence and Outcomes substudies. With a support system in place for the long-term follow-up of patients, the Miami ACTU anticipates to enroll approximately 80 patients into the ALLRT study (ACTG 5001) over a 2-year period.

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- **Project Title: MIDCAREER INVESTIGATOR AWARD IN NEURO-AIDS RESEARCH**

  Principal Investigator & Institution: Simpson, David M.; Professor; Neurology; Mount Sinai School of Medicine of Nyu of New York University New York, Ny 10029

  Timing: Fiscal Year 2001; Project Start 01-JAN-2001; Project End 31-DEC-2005

  Summary: (Adapted from the Applicant's Abstract): This application proposes David Simpson M.D. for a Mid-Career Investigator Award in Patient-Oriented Research in Neuro-AIDS. Its primary focus is to provide the Principal Investigator with support to continue his development as a productive clinician/scientist with sufficient protected time to pursue his clinical research and mentoring activities. As the first emphasis of this proposal, the Candidate proposes to continue and intensify a program of patient-oriented research, focused on the neurological disorders complicating HIV infection and AIDS. The objective is to build a clinical research program in Neuro-AIDS that engages the participation o researchers from a variety of clinical disciplines to address the multi-faceted aspects of HIV-associated neurological disorders. A primary focus of proposed new research is the prospective and longitudinal assessment of patient cohorts with advanced HIV disease in order to identify subclinical and unrecognized neurological disorders. Specific disorders of interest include **peripheral neuropathy** associated with HIV infection and neurotoxic antiretroviral agents, myopathy, myelopathy, and cognitive impairment. Outcomes of interest include risk factors for the development of these disorders, their correlation with virological and immunological measures, and the utility of assessment instruments. Cohorts available for these studies include the NIH-funded Manhattan Brain Bank Consortium, AIDS Clinical Trials Group studies, and pharmaceutical industry trials. Patients identified with neurological disorders will be referred into ongoing therapeutic clinical trials. The second emphasis of this proposal is the mentoring of Fellows and Junior Faculty committed to patient-oriented research. Trainees will be recruited from numerous disciplines including Neurology, Infectious Diseases and non-physician health care providers, including Nurse Practitioners and Physician Assistants- Visiting Scholars from abroad will be mentored. The Program will provide a structured curriculum incorporating a knowledge base in Neuro-AIDS, neurological examination skills, and training in clinical trial design, conduct, and

analysis. The Neuro-AIDS Educational Program will incorporate an Internet-based and video case presentation series in order to provide distance learning for health care providers, patients and other communities. The Neuro-Adherence Program will assess the affect of neurological disease on patients' adherence to medical regimens, and the impact of education and support groups on adherence.

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- **Project Title: MODULATION OF CONNEXIN CHANNEL ACTIVITY**

  Principal Investigator & Institution: Harris, Andrew L.; Associate Professor; Pharmacology and Physiology; Univ of Med/Dent Nj Newark Newark, Nj 07103

  Timing: Fiscal Year 2001; Project Start 01-SEP-1999; Project End 31-AUG-2003

  Summary: (from applicant's abstract): The physiology of intercellular Signaling through gap junctions is still a mystery. In spite of considerable progress in connexin biochemistry, and genetics, the ligands that directly control whether the channels are open or closed are unknown. Identification of fhe cytoplasmic factors that interact directly with connexin channels, and how they modulate channel activity, are fundamental unsolved issues with far-reaching impact. Gap junction channels (composed of connexin) are regulated pathways for intercellular movement of ionsn and small molecules. Their location constrains their study in situ; both ends of the pore are intracellular, inaccessible to most used to explore channel function. Since access to the channel is via cytoplasm, it is difficult to identify factors that act directly on the channel, rather than via cellular components. The long-term goal is to understand the molecular operation of this pathway of intercellular signaling. The approach is to study connexin channels in a reconstituted system where their modulation can be readily explored. Channels formed by connexin32 and connexin26 immunopurified from native tissues and expression vectors will be studied in a well-characterized system that yields information that cellular studies cannot. The experiments build on preliminary studies that have identified, for the first time, compounds that interact directly and noncovalently with connexin channels to modulate their activity. The proposed studies address the questions: What is the molecular basis for the action of protonmated aminosulfonates such as taurine on connexin chanel activity? What is the molecular basis of the high-affinity inhibition of connexin channels by the high-affinity inhibition of connexin channels by cAMP and cGMP? What parts of connexin molecules interact with these compounds? Why do the two connexins respond differently? What can be learned about connexin structure-function when derivatives of these compounds are' used as affinity reagents? By study of connexin channels in this experimentally accessible system, one hopes to understand the fudamental properties of intercellular signaling. Gap junctions are so widespread that elucidation of connexin channel activity modulation will have profound consequences throughout cellular and developmental biology. There are over 18 known connexins. In humans, genetic defects in connexin32 cause a **peripheral neuropathy,** and in connexin26 cause a large fraction of nonsyndromic deafness. No doubt many other syndromes anise in toto or in part from defects in connexin channel function. Such defects will result in abnormal (i.e., greater or lesser) intercellular signaling molecules. The proposed studies address how this may occur.

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- **Project Title: MODULATION OF PRIMATE SOMATOSENSORY CORTICAL RESPONSES**

  Principal Investigator & Institution: Nelson, Randall Jay.; Professor; Anatomy and Neurobiology; University of Tennessee Health Sci Ctr Health Science Center Memphis, Tn 38163

  Timing: Fiscal Year 2001; Project Start 01-JUL-1997; Project End 30-JUN-2006

  Summary: Through neurophysiological experiments, we will determine how sensory responses and movement-related activity is dynamically altered during three types of purposeful hand movements. Specific Aim number 1 is to determine if somatosensory signals can be detected at times before movements when sensory gating is thought to occur, and if this detection depends on the modality of stimuli previously used to trigger movements. Specific Aim number 2 is designed to test changes in responsiveness gain before, during and after changes in visual feedback gain. Specific Aim number 3 is designed to test the modulation of sensory responsiveness with changes in the type of prior information about the task. Each experiment will determine when sensorimotor cortical neuronal activity is more tightly coupled to sensory stimuli and movement kinematics. Three hypotheses will be tested: that (1) Sensory stimuli requesting behavioral changes are less effective in altering movements if presented near movement onset or if other somatosensory stimuli have been presented previously, that (2) Sensory responses are better entrained to vibratory stimuli and movement-related activity is more tightly coupled to movement kinematics when the gain of visual feedback for movement to targets is abruptly changed, and that (3) Knowing where, but not in which direction, tracking-target deviations occur results, in suppression of most peripheral inputs that are time-locked to predicted tracking- target deviation onset, while knowing in which direction but not where (and thus when) a tracking-target deviation will occur results in a gradual increase the suppression of certain peripheral inputs. The underlying central hypothesis is that external sensory information is utilized as needed to guide behavior and suppressed when redundant or competitive. These hypotheses will be tested, using single electrodes and possibly multi-electrode arrays to record extracellular activity in the primary somatosensory, parietal (area 5 and 7b), primary motor and premotor (PMd) cortices of awake, behaving monkeys trained to perform wrist movement tasks. Coupling of activity to sensory stimuli will be assessed by mean vector analyses. Movement kinematics will be correlated with neuronal activity using multiple regression analyses. The three behaviors to be studied could be used during retraining when sensory disorders occur following stroke, traumatic head injury, **peripheral neuropathy** and movement disorders. By understanding how and where somatosensory responsiveness is modified during behavior, deficits can be more readily assessed and localized.

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- **Project Title: MOLECULAR MECHANISMS OF SPINAL CORD PLASTICITY**

  Principal Investigator & Institution: Brock, John H.; Neurobiology; Mount Sinai School of Medicine of Nyu of New York University New York, Ny 10029

  Timing: Fiscal Year 2002; Project Start 01-AUG-2002

  Summary: (provided by applicant): Promoting functional recovery to CNS or PNS injury requires maximizing neuronal survival, facilitating axon growth, remyelination and appropriate synapse formation. This last step is particularly important since formation of new synapses with inappropriate targets could produce maladaptive consequences. Tactile allodynia, characterized by hypersensitivity to innocuous mechanical stimuli, is

associated with **peripheral neuropathy** and has been attributed to the central sprouting of A13 fibers (low threshold mechanoreceptors) into the superficial dorsal horn of the spinal cord, where they form functional synapses with nociceptive neurons that normally relay painful stimuli. We are interested in identifying the molecules and elucidating the mechanisms that enable axon sprouting and aberrant synapse formation.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: MOLECULAR PATHOGENESIS OF MNGIE**

  Principal Investigator & Institution: Hirano, Michio; Assistant Professor; Columbia University Health Sciences New York, Ny 10032

  Timing: Fiscal Year 2003; Project Start 01-DEC-2002; Project End 30-NOV-2007

  Summary: Mitochondria are the main sources of energy in the cell. They are unique mammalian organelles because they contain their own DNA (mtDNA), whose genes encode components of the respiratory chain/oxidative phosphorylation system. They are essential for the normal functioning of all cells in the body, and are absolutely critical for the function of those tissues that are highly dependent on aerobic metabolism, including heart, skeletal muscle, and brain. Since 1988, single large-scale mtDNA rearrangements, more than 100 mtDNA point mutations, as well as mendelian-inherited multiple mtDNA deletions have been associated with human diseases. Mitochondrial neuro-gastrointestinal encephalomyopathy (MNGIE) is an autosomal recessive disorder associated with multiple deletions and depletion of mtDNA in skeletal muscle. The major clinical features are: ptosis, external ophthalmoparesis, gastrointestinal dysmotility, cachexia, **peripheral neuropathy,** and leukodystrophy. We mapped the disease to chromosome 22q13.32-qter and subsequently identified loss-of-function mutations in the thymidine phosphorylase (TP) gene as the cause of the disorder. With the support of a NIH grant, we have continued our investigation of MNGIE. Clinicians from around the world have sent us blood samples to test for defects in thymidine phosphorylase. To date, we have identified 51 MNGIE patients. All patients tested have shown very low or no detectable activity of thymidine phosphorylase in huffy coat samples. In addition, we have identified dramatic increases of thymidine levels in plasma from patients. These findings led us to hypothesize that elevated intracellular levels of thymidine cause alterations of mitochondrial nucleotide pools that, in turn, induce point mutations, multiple deletions, and depletion of mtDNA. To test our hypothesis, we propose to study this disorder in vivo using human autopsy samples and in vitro using fibroblasts from patients. In addition, we have produced thymidine phosphorylase knock-out mice as a model for MNGIE. Our proposed studies of the pathogenesis of MNGIE are likely to enhance our understanding of nucleotide metabolism and will likely lead to more rational therapies for this uncommon, but devastating illness.

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- **Project Title: MOLECULAR STUDIES IN C/M/T DISEASE TYPE 4 B AND C**

  Principal Investigator & Institution: Ben Othmane, Kamel; Neurology; Virginia Commonwealth University Richmond, Va 232980568

  Timing: Fiscal Year 2001; Project Start 01-DEC-1996; Project End 30-NOV-2002

  Summary: Charcot-Marie-Tooth disease (CMT) is a common **peripheral neuropathy** with different modes of inheritance and extensive genetic heterogeneity. Significant progress has been made in the elucidation of the molecular defects of autosomal dominant forms leading to the identification of several peripheral nerve proteins (PMP-

22, PO, and Connexin 32). The goal of this proposal is to employ similar positional cloning techniques to identify the defects for two different forms of autosomal recessive CMT (CMT4B and C). We have previously collected a large series of CMT4 families and proposed an improved classification into three types A, B, and C. In addition, we demonstrated linkage of one group: CM4A to chromosome 8q21. Subsequently, we have shown that CMT4B and CMT4C do not map to this chromosomal region. Large inbred CMT4B and CMT4C families will be genotyped for chromosomal localization using linkage analysis. Once a linkage is detected, a YAC and a PAC contig will be initiated across the region. Using the contig, we will generate additional repeat markers in the region. Key recombination events and linkage disequilibrium will be investigated to further narrow the disease flaking interval. The Direct selection technique will subsequently be used to construct a transcription map in the region allowing for candidate genes to be tested for mutations.

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- **Project Title: MOLECULAR STUDIES OF DOMINANT AUTOSOMAL SPASTIC PARAPLEGIA (SPG)**

  Principal Investigator & Institution: Marchuk, Douglas A.; Duke University Durham, Nc 27706

  Timing: Fiscal Year 2001

  Summary: Hereditary Spastic Paraplegia (SPG; OMIM 182600) comprises a group of neurodegenerative disorders characterized by progressive spasticity of the lower limbs. SPG has been classified into pure (uncomplicated) and complex (complicated) forms based on clinical symptoms; patients with complicated SPG exhibit in addition to spasticity of the lower limbs other neurological symptoms, such as mental retardation, retinal changes, **peripheral neuropathy,** and ataxia. Decreasing age of onset and/or increasing severity in successive generations has also been noted, suggesting anticipation of SPG symptoms. SPG is genetically heterogeneous; autosomal dominant "uncomplicated" SPG families show locus heterogeneity, with linkage reported to chromosomes 2p (SPG4), 14q (SPG4), 14q (SPG3), and thus far a single kindred mapping to 15q (SPG6). A number of studies including our own suggest that the majority of most families are linked to chromosome 2p. In addition, anticipation has been reported for the chromosome 2 locus. Families unlinked to any of the three known loci have also been reported, suggesting that at least one additional major SPG locus. The minimum candidate regions (MCR) reported for SPG4 and SPG3 are a 3 cM interval between D2S352 and D2S367 and a 7 cM interval between D14S288 and D12S281, respectively. The purpose of this project is to continue our longstanding genetic analysis of autosomal dominant SPG. We will prioritize these studies by first attempting to positionally clone the SPG4 locus on chromosome 2p. Once identified we will carry out mutation analysis and phenotype/genotype correlations in conjunction with Cores B and C. Positionally cloning of additional SPG will commence upon successful completion of our chromosome 2 work. In addition, we propose to identify in conjunction with Core C other loci using our unlinked families.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE IN SOUTHEASTERN MINNESOTA**

  Principal Investigator & Institution: Kyle, Robert A.; Mayo Clinic Rochester 200 1St St Sw Rochester, Mn 55905

Timing: Fiscal Year 2001

Summary: The objective of this research is to determine the natural history of monoclonal gammopathy of undetermined significance (MGUS). We will determine the prevalence of MGUS among Olmsted County, MN residents aged 50 years or greater (estimated population 26,022). We will obtain samples on most of the population in the course of their medical care. We will then contact the remaining residents by mail in an attempt to enroll them into the study as well. In order to ascertain the long-term outcome, we will also conduct a retrospective cohort study of survival and risk of multiple myeloma, macroglobulinemia, primary amyloidosis, and other plasma cell proliferative disorders in all cases of MGUS from the entire Southeastern Minnesota region (including Olmsted County) first diagnosed between January l, 1960 and December 31, 1997. We will follow the January l, 1998 survivors of the Southeastern Minnesota MGUS cohort including any asymptomatic prevalence cases and all subsequent newly diagnosed cases in a prospective study to assess predictors of outcome such as development of multiple myeloma or related disorders. The incidence of a variety of malignant and nonmalignant disorders will be determined in all MGUS patients in Southeastern Minnesota and a control cohort. Nurse abstractors will carefully review the Mayo Clinic records from 1960 through 1997 of all MGUS patients in Southeastern Minnesota for evidence of nonplasma cell neoplasms such as carcinoma or leukemia. Nonmalignant disorders consisting of hematologic diseases including pernicious anemia, idiopathic thrombocytopenic purpura, polycythemia vera, and myelodysplastic disorders will be evaluated as will connective tissue diseases including rheumatoid arthritis, lupus erythematosus, polymyalgia rheumatica, temporal arteritis, and ankylosing spondylitis. Neurologic disorders will include sensorimotor **peripheral neuropathy,** amyotrophic lateral sclerosis, and myesthenia gravis. Dermatologic diseases such as pyoderma grangrenosum, necrobiotic xanthogranuloma, lichen myxedematosus, Sezary syndrome, mycosis fungoides, and Kaposi's sarcoma will be sought. The presence of immunosuppression from HIV or transplants will be reviewed. Patients with liver disease, especially hepatitis C, will be included. This study will also provide bone marrow and peripheral blood for Projects II, III, IV, and V in an effort to better understand the biology of MGUS and multiple myeloma.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: NEURAL CONTROL OF POSTURE AND STANCE**

  Principal Investigator & Institution: Macpherson, Jane M.; Senior Scientist; None; Oregon Health & Science University Portland, or 972393098

  Timing: Fiscal Year 2001; Project Start 15-JUL-1991; Project End 31-MAY-2003

  Summary: The long-term goal of the research is to better understand the neural control of posture and balance. Adequate control of posture is vital for the performance of functional motor tasks, yet little is understood about the sources of sensory feedback and their integration in balance control. The studies in this proposal focus on the role of somatosensory afferents in balance using a novel model of peripheral sensory neuropathy, in which a high dose of pyridoxine (vitamin B6) is used to induce widespread deafferentation. This approach has the potential to reveal new and significant information about the role of somatosensation in motor control. The role of somatosensory afferents in the control of posture and balance is unclear. Specific aims 1 and 2 will examine the role of somatosensory inputs in: 1) the automatic postural response to unexpected disturbances of stance, 2) the anticipatory postural adjustment that accompanies voluntary movements. Specific aim 3 will determine the temporal sequence and spatial pattern of large fiber deafferentation induced by pyridoxine at

both the functional and the morphological levels. Our preliminary data show that the loss of large diameter afferent fibers that is induced by pyridoxine toxicity results in a significant delay of the automatic postural response to sudden movements of the support surface during stance. This observation is very exciting because it may lead to the first clear demonstration that somatosensory inputs are critical for triggering of the early, automatic postural response. **Peripheral neuropathy** is a significant health problem not only as a result of common syndromes such as diabetes but also as part of the aging process. Clinical neuropathies often have mixed motor and sensory fiber involvement. The loss of either motor or sensory fibers or both could result in ataxia and balance difficulties with the associated risk of falling. The studies in this proposal will provide a clearer understanding of the role of somatosensory afferents in balance and thereby may suggest better diagnostic tools for evaluating the mechanism of a balance disorder in patients with **peripheral neuropathy.** Further, this understanding may lead to new ideas and rehabilitation techniques for improving balance in these patients.

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- **Project Title: NEUROBIOLOGY OF DISEASE -- TEACHING WORKSHOP**

  Principal Investigator & Institution: Lipton, Stuart A.; Director, Degenerative Disease; Society for Neuroscience 11 Dupont Cir Nw, Ste 500 Washington, Dc 20036

  Timing: Fiscal Year 2001; Project Start 01-AUG-1983; Project End 31-MAY-2006

  Summary: The Society for Neuroscience (SFN) is the major professional organization for scientists who study the nervous system. An important goal of this organization is to encourage scientists in training to undertake research related to diseases of the nervous system. The objective of this grant application is to support teaching workshops that introduce young neuroscientists to current concepts about the etiology and pathogenesis of disorders of the nervous system. For each workshop, about 12 faculty are chosen by the Organizing Committee after eliciting proposals from the Society at large. Clinical presentations provide enrollees with an experience of the human dimension of particular diseases. Lectures cover both clinical research and relevant laboratory work. In addition to lectures, enrollees are given a choice of attending two of four small group workshops that emphasize either specific or methodological issues and encourage lively discussion. Since its inception, 20 workshops have been held, usually on the day prior to the start of the Society for Neuroscience meeting. Topics have included: Infections in the nervous system, epilepsy, Huntington's and Alzheimer's diseases, muscular dystrophy, multiple sclerosis, prion diseases, drug addiction, pain and affective disorders, stroke and excitotoxicity, neuromuscular diseases, amyotrophic lateral sclerosis, schizophrenia, migraine, mental retardation and developmental disorders, Tourette's syndrome and obsessive-compulsive disorder, and the neurobiology of brain tumors. Enrollment generally runs between 100 and 200 attendees. Most enrollees are graduate students or postdoctoral fellows. Current plans are to cover the following topics in the near future: Genes, free radicals, mitochondria and apoptosis in Parkinson's disease, AIDS dementia, **peripheral neuropathy,** pain, language disorders, and affective disorders. Other topics will be chosen depending on their potential interest to young neuroscientists, their impact on society and the quality of recent research related to that disease area. We are especially interested in covering diseases of the nervous system which are important clinically but which are in need of enhanced basic cellular and molecular understanding. Society members are encouraged to suggest topics in the SFN Newsletter.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: NEUROLOGIC AIDS RESEARCH CONSORTIUM**

  Principal Investigator & Institution: Clifford, David B.; Professor and Head; Neurology; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

  Timing: Fiscal Year 2003; Project Start 01-MAY-1997; Project End 30-APR-2008

  Summary: The Neurologic AIDS Research Consortium (NARC) will maintain an effective collaborative clinical study group dedicated to the study of HIV-associated neurologic disease. Projects are identified by investigators, designed with review by internal and external experts and implemented. This proposal includes completion of currently active studies, and initiation of new areas of investigation relevant to the neurologic complications associated with HIV infection. The specific projects to be undertaken include: 1. Complete and analyze A5090 testing the safety and efficacy of transdermal selegiline for HIV- associated motor cognitive disorder; 2. Monitor the incidence, prevalence and natural history of HIV related neuropathy and neuropsychologic disorders and validate brief screens for detection of central and peripheral nervous system dysfunction in the Adult Longitudinal Linked Retroviral Treatment (ALLRT) Cohort of the AIDS Clinical Trial Group; 3. Complete and analyze longitudinal physiologic and morphologic characterization of distal sensory neuropathy in HIV over a one year period of observation; 4. Complete and analyze our study of the virologic, immunologic and pharmacologic manifestations of HIV in CSF compartment during anti-retroviral treatment; 5. Perform a study of Acetyl L-carnitine for treatment of dideoxynucleoside induced painful neuropathy in HIV infection; 6. Develop and implement a study to measure the safety, tolerability and analgesic properties of Prosaptide for HIV-associated painful **peripheral neuropathy;** and 7. Characterize the newly described acute neuromuscular disorder associated with lactic acidosis seen in treated HIV patients. Major studies will be developed and operated cooperatively with the AIDS Clinical Trial Group (ACTG). The NARC will continue to develop a broad agenda for clinical study of neuroAIDS complications following these studies, directed by the Principal Investigator, Executive Steering committee and the NINDS appointed Data and Safety Monitoring Board (DSMB).

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- **Project Title: NEUROPATHY IN YOUNG PUERTO RICAN DIABETICS**

  Principal Investigator & Institution: Luciano, Carlos A.; University of Puerto Rico Med Sciences Medical Sciences Campus San Juan, Pr 00936

  Timing: Fiscal Year 2001

  Summary: Peripheral neuropathy is a common complication of diabetes associated with significant morbidity and increased mortality. Although the increased risk for development of neuropathy associated with long- standing diabetes has been well documented, the frequency and types of neuropathy developing in the early years after the diagnosis of diabetes has not been well studied. Furthermore, there are no studies specifically focusing on young (children and adolescent) Hispanic diabetics as a distinctive cohort in spite of the high frequency of both type I and type II diabetes. Our long-range goal is to develop methods for the prevention and treatment of the various types of Diabetic Neuropathy affecting the Puerto Rican population. Our current objective is to determine the frequency of the different types of diabetic neuropathy in young Puerto Rican diabetics, and examine the association of neuropathy with factors that may contribute to the development of neuropathy. Our central hypothesis is that the prevalence of diabetic neuropathy is greater in young Puerto Rican diabetics and is associated with ethnic-specific risk factors, different from those observed in other

ethnically and genetically different populations. The rationale for the proposed study is that determining the prevalence of the individual types of diabetic neuropathy is the first step in identify potential risk factors present in Puerto Rican diabetics, and in devising this study. Specific Aim 1: Determine the frequency of neuropathy-associated symptoms, signs and functional abnormalities of nerve fibers. Specific Aim 2: Determine the frequency of putative risk factors associated with the different types of diabetic neuropathy in this subpopulation. The proposed research will allow us to understand what is the relationship between the high frequency of diabetes and the development of neuropathy in this high-risk population.

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- **Project Title: NEUROPOIETIC CYTOKINES IN DIABETIC PERIPHERAL NEUROPATHY**

  Principal Investigator & Institution: Banner, Lisa R.; California State University Northridge 18111 Nordhoff St Los Angeles, Ca 91330

  Timing: Fiscal Year 2002

  Summary: (provided by applicant): One of the most common manifestations of diabetes mellitus is damage to the peripheral nervous system, known as diabetic neuropathy. While the precise mechanism responsible for the development of neuropathy has yet to be elucidated, it is mostly likely mediated by a variety of metabolic responses. Increasing attention has been directed at studying molecules that mediate growth and survival of the nerves, and has focused on some classical proteins such as nerve growth factor. We believe an additional group of mediators, known as cytokines, are also involved in this process. We are interested in a specific family of cytokines, the neuropoietic cytokine family, because its members are known to be expressed by both the nervous and immune systems and in the peripheral nervous system, at least three members of this family are important in the response to injury and repair in normal animals. We will investigate cytokine expression during the onset of neuropathy and in response to nerve injury. In addition, we will ask whether nerve regeneration is altered by administration of these cytokines. This could have obvious health benefits to the millions of diabetics that suffer from nerve damage.

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- **Project Title: NEUROTROPHIC FACTOR RESPONSIVENESS DIABETIC NEUROPATHY**

  Principal Investigator & Institution: Twiss, Jeffrey L.; Pathology; University of California Los Angeles 10920 Wilshire Blvd., Suite 1200 Los Angeles, Ca 90024

  Timing: Fiscal Year 2001; Project Start 30-SEP-2000; Project End 31-AUG-2002

  Summary: (Applicant's abstract): Decreased neurotrophic support has been postulated as a cause of diabetic **peripheral neuropathy** and exogenous neurotrophic factors have shown some promise for treatment of this diabetic complication. Levels of some neurotrophic factors are decreased in diabetic animals. There is also reason to believe that responsiveness to neurotrophic. factors is altered in diabetes mellitus. The objective of this proposal is to address the role of neurotrophic responsiveness in the pathogenesis of diabetic **peripheral neuropathy.** In Specific aim I, we will directly test the intracellular responsiveness of sensory neurons from diabetic rodents to exogenous and endogenous neurotrophins. Application of exogenous NGF and BDNF will show whether the diabetic sensory neurons can initiate appropriate intracellular signaling mechanisms in response to these neurotrophins. Autocrine/paracrine-produced BDNF

supports survival of adult sensory neurons in vitro. Curiously, BDNF mRNA is actually increased in sensory ganglia of diabetic animals, raising the question of whether these neurons can respond to BDNF. Responsiveness of these sensory neurons to endogenous BDNF will be determined by selectively inhibiting the BDNF receptor (TrkB) or competitively removing BDNF from the culture medium. The loss of activity of TrkB and downstream signaling pathways (Ras-Erk and P13K-Akt) will provide a measure of the capacity of diabetic sensory neurons to maintain intracellular signaling mechanisms in response to neurotrophins. In Specific Aim II, we will address the molecular responsiveness of diabetic sensory neurons to the endogenous neurotrophic factors that are increased after nerve injury. Altered neurotrophic factor responsiveness both before and after nerve injury may indeed account for the aborted nerve regeneration seen in diabetic animals. We will use conditioning crush lesions to determine if diabetic sensory neurons can i) generate a population of mRNAs needed for axonal regeneration after nerve injury, and ii) regulate the translation of these mRNAs to rapidly extend axons in vitro.

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- **Project Title: NUTRITION AND VIRUS INDUCED OPTIC NEUROPATHY**

  Principal Investigator & Institution: Beck, Melinda A.; Associate Professor; Pediatrics; University of North Carolina Chapel Hill Office of Sponsored Research Chapel Hill, Nc 27599

  Timing: Fiscal Year 2001; Project Start 15-APR-1999; Project End 31-MAR-2003

  Summary: The effect(s) of nutrition on viral disease has not been well studied. The currently accepted model for the influence of nutrition on viral pathogenesis invokes host factors, such as a decreased immune response, which are responsible for the increased susceptibility of malnourished individuals to disease. However, little attention has been focused on the pathogen itself, which is replicating in a nutritionally deficient host. Previous work in our laboratory demonstrated that increased oxidative stress in a coxsackievirus-infected mouse, due to a dietary deficiency in either selenium or vitamin E, led to mutations in a normally avirulent strain of coxsackievirus, causing it to become virulent. Once the avirulent virus had mutated in the nutritionally deficient host, it could now cause disease even in hosts with normal nutriture. Thus, we showed for the first time that the nutritional status of the host can have a profound effect on the genome of a virus, changing an avirulent virus to a virulent one. For this application, we propose to study the outbreak of optic and/or **peripheral neuropathy** which occurred in Cuba in the early 1990's. The disease was associated with major changes in the Cuban diet resulting in decreases in vitamins A, B complex and E and selenium, with smoking as a co- factor. In addition to the nutritional deficiency, a coxsackie- like virus was isolated from the cerebrospinal fluid of 105 out of 125 patients tested, suggesting a co-factor role for this virus in the etiology of the disease. Again, the virus was altered compared to the prototype coxsackievirus from which it may have arisen, and the clinical syndrome differed from those previously associated with coxsackievirus infections of the central nervous system. We have sequenced one variant isolate from a patient diagnosed with nutritionally-induced optic neuropathy and found that although it is closely related to coxsackievirus A9, mutations in various regions of the virus suggest that alterations in its pathogenic expression is possible. We propose to use the Cuba epidemic as a model for a viral disease induced by a nutritional deficiency. We propose to use sequence analysis to study the evolution of the variant virus during the epidemic of optic neuropathy in order to understand the role of nutrition in the emergence of this disease. In addition, we will utilize cell culture techniques to further dissect the mechanism by

which the viral mutations occur. Taken as a whole, we believe these studies will provide important new information on the critical role nutrition plays in the development of new viral variants with unpredictable pathogenic properties, a long neglected area of study.

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- **Project Title: OPTIMAL OFF-LOADING THERAPY FOR HEALING DIABETIC ULCERS**

  Principal Investigator & Institution: Sinacore, David R.; Associate Professor; Physical Therapy Education; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

  Timing: Fiscal Year 2001; Project Start 01-APR-2001; Project End 31-MAR-2005

  Summary: (adapted from the application) Foot ulcers in people with diabetes mellitus represent a major public health problem of increasing magnitude and escalating health care expenditure. Diabetic foot ulcers are frequently due to a combination of **peripheral neuropathy,** minor trauma, peripheral vascular disease and accompanying foot deformity which often lead directly to lower extremity amputation (LEA) Currently, total contact casting (TCC) is the most rapid and effective method for healing diabetic neuropathic foot ulcers. TCC has several major drawbacks including requiring specialized skills in the application, patient reports of difficulties with walking and ADL function and frequent cast changes to prevent complications. These limitations have prevented its wide-spread adoption as the optimal off-loading therapy. Recently, some removable ankle foot orthoses (AFOs) have been shown to reduce plantar pressures to a similar extent as TCC, though ulcer healing outcomes have not yet been demonstrated. Removable AFOs offer many potential advantages over TCC such as lower costs, easier patient application and greater convenience by requiring fewer visits to health care specialists. The overall goal of this application is to conduct a prospective, randomized controlled clinical trial comparing TCC to a removable AFO to determine the optimal off-loading therapy for healing diabetic, neuropathic foot ulcers. The Specific Aims of this project are to determine the percent of subjects with Wagner grade 1 or 2 neuropathic foot ulcers who completely heal within 8 weeks; and the time (in days) it requires to achieve complete healing using each off-loading therapy. Additional aims will be to determine the impact each off-loading therapy has on subjects' level of impairment, functional limitation, disability and to determine the costs and cost-effectiveness associated with each offloading therapy based on discrete indicators of patient severity and compliance to each therapy. The results of this application will have an immediate impact toward increasing our current understanding of the magnitude of pressure offloading which is required to achieve successful healing outcomes. In addition, we will define the optimal off-loading therapy for rapid and effective ulcer healing outcomes which promise to reduce the annual number of LEAs, limit the burden of disability and demonstrate the most cost-effective pressure off-loading therapy in patients with diabetes mellitus and chronic foot ulcers.

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- **Project Title: P0-MEDIATED SIGNALING AND MYELINATION**

  Principal Investigator & Institution: Lilien, Jack E.; Professor; Biological Sciences; University of Iowa Iowa City, Ia 52242

  Timing: Fiscal Year 2003; Project Start 01-FEB-2003; Project End 31-JAN-2007

Summary: (provided by applicant): Myelin is a multilamellar membrane that surrounds axons in both the central and peripheral nervous system P0, a member of the immunoglobulin family of adhesion molecules, is the most abundant protein in peripheral myelin and is thought to mediate adhesion between the multiple layers of myelin as they wrap around the axon. Consistent with an important role for P0 in myelination, mutations in both the extracellular and intracellular domains cause the human **peripheral neuropathy** Charcot-Marie-Tooth disease type 1B. Our long-range goals are to couple basic and clinical research to discover the molecular basis for P0 function in human myelination. We have recently discovered that point mutations in a Protein Kinase C (PKC) target motif - RSTK - in the cytoplasmic domain of P0 abolish its adhesive function, as does inhibition of PKC. We have also identified a CMT1B patient with a mutation in the RSTK motif (R to S), further indicating the importance of PKC-mediated phosphorylation in myelination. The goals of this proposal are to determine the role of PKC-mediated phosphorylation in adhesion and myelination. 1) We have found that RACK1, the Receptor for Activated C Kinase is a component of the complex of proteins associated with the cytoplasmic domain of P0. We will determine if RACK1 or other adapters are needed to target PKC to the cytoplasmic domain of P0. We will further characterize the domains through which partners interact using deletion constructs in conjunction with the two-hybrid system and/or an in vitro binding assay 2. By analogy with other adhesion molecules, we hypothesize that phosphorylation creates a binding site for adaptors or effectors essential for the interaction of P0 with downstream targets. We have identified one protein whose interaction with P0 depends on phosphorylation of serine in the RSTK motif using the yeast two-hybrid system. We will characterize the binding of this component and downstream targets. 3) We will evaluate the role of each of the components identified in aims 1 and 2 using an in vitro myelination culture system by introducing dominant-negative and constitutively active constructs, as well as constructs coding for peptide competitors for critical protein-protein interactions, into Schwann cells prior to co-culture with neurons.

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- **Project Title: PACLITAXEL INDUCED PAINFUL PERIPHERAL NEUROPATHY IN RATS**

  Principal Investigator & Institution: Polomano, Rosemary C.; Assistant Professor; Anesthesia; Pennsylvania State Univ Hershey Med Ctr 500 University Dr Hershey, Pa 17033

  Timing: Fiscal Year 2001; Project Start 01-MAY-2000; Project End 30-APR-2003

  Summary: The principal investigator, Rosemary C. Polomano, PhD, RN, intends to pursue a career as an independent, clinical and laboratory investigator in biobehavioral pain research in a health system with an academic appointment in a school of nursing and medicine. Intensive laboratory training combined with academic study in neuroscience will enable the principal investigator to examine and better explain the neurophysiological basis for pain associated with paclitaxel neurotoxicity. The primary aim of this investigation is to develop a painful neurotoxicity model appropriate for human disease, and to effectively translate the findings to human experiences. Painful manifestations from paclitaxel-induced neuropathy will be measured by abnormalities in responses to thermal- (heat and cold) and mechano- (touch and pressure) stimuli in the rats' hind paws and tails that result from damage to the small primary or sensory afferent fibers. This model will advance the development and testing of possible strategies for pain prevention and control, thus increasing the usefulness of this highly effective antineoplastic drug. Graded dosing schedules of paclitaxel or a control vehicle

will be administered to 280 male Sprague-Dawley rats in order to find one that produces the greatest degree of a painful **peripheral neuropathy,** without reaching the threshold for damage to motor fibers or systemic toxicity. Specifically, this investigation will 1) demonstrate and quantify the onset, duration and severity of painful **peripheral neuropathy** in rats treated with intraperitoneal paclitaxel by measuring behavioral responses (i.e., thermal- and mechano-hyperalgesia and cold- and mechano- allodynia) in the hind paw and tail and motor coordination, and electrophysiological changes in the hind leg nerves following sequential doses, 2) compare differences in the severity of pain- evoked responses for the four paclitaxel dosing schedules to determine if single-dose intensity of cumulative (total) dose produces the greatest sensory abnormalities, and 3) correlate sensory abnormalities in small myelinated (A-delta) and unmyelinated (C-) fibers to the presence and severity of anatomical changes in the nerves and serum peak levels of paclitaxel. Chemotherapy-induced peripheral neurotoxicity is a problem that will only worsen as advances in granulocyte-colony stimulating factor now permit more aggressive therapy with potentially neurotoxic agents. Greater attention has been placed on understanding peripheral sensory and motor neuropathies associated with chemotherapy because these conditions compromise quality of life. As concerns over quality of life and the long- term effects of cancer treatment among survivors grow and clinicians struggle with ways to manage these effects, animal models will become a vital line of inquiry into the scientific basis for etiologies and treatment strategies.

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- **Project Title: PATHOGENESIS OF HEREDITARY TRANSTHYRETIN AMYLOIDOSIS**

  Principal Investigator & Institution: Benson, Merrill D.; Professor; Molecular and Medical Genetics; Indiana Univ-Purdue Univ at Indianapolis 620 Union Drive, Room 618 Indianapolis, in 462025167

  Timing: Fiscal Year 2001; Project Start 01-AUG-1990; Project End 31-MAR-2004

  Summary: (from abstract): The overall objective of this proposal is to define the pathophysiology of the autosomal dominant transthyretin amyloidoses. These diseases, while considered rare, are actually being recognized in increased numbers of kindreds throughout the world and especially in the United States. Transthyretin amyloidosis is usually associated with **peripheral neuropathy,** nephropathy, and cardiomyopathy which present as late-onset (adult) disease with high degrees of morbidity and mortality. To date at least 72 variants of transthyretin (TTR) have been found to be associated with systemic amyloidosis which is inherited as an autosomal dominant disease. Of particular concern is the fact that: 1) it has recently been shown that there are elderly individuals who develop transthyretin amyloid cardiomyopathy (senile cardiac amyloldosis) in the absence of any detectible mutation in transthyretin; and, 2) there is a high prevalence of one particular transthyretin mutation (isoleucine 122) in the American Black population and this is manifest as amyloid cardiomyopathy. These two findings suggest that, as the population ages, amyloid heart disease will become of greater significance to the American population. Previous studies have centered on determining structural changes of transthyretin which are related to amyloid formation. Structures of amyloid forming variants methionine 30, serine 84, alanine 60, arginine 10, tyrosine 77 have been compared to structures of non amyloid forming threonine 109, serine 6, methionine 119 and normal transthyretin. No common structural change has been found to explain initiation of the fibril forming process but preliminary data suggest that solvent accessability to variant transthyretin dimers may allow a proteolysis event which could lead to the initiation of fibril formation. Metabolic studies

using radiolabelled variant and normal transthyretins have suggested increased plasma clearance of variant proteins. The Specific Aims will test the hypothesis that single amino acid substitutions in transthyretin result in changes in tertiary structure of the transthyretin molecule which allow alterations in metabolism of the variant molecule and its associated normal monomers to lead to amyloid formation. Transthyretin proteins isolated from tissues of patients with amyloidosis will be studied to characterize proteolytic peptides and determine if partial proteolysis with generation of carboxyl terminal peptides is a factor in amyloid fibril formation. Fibril forming potential of these fragments will be tested by producing recombinant protein of residues 49 - 127 and testing fibril formation with and without full-length transthyretin in vitro. A new Specific Aim will test the hypothesis that the ratio of the various tetrameric forms of transthyretin affects the propensity to form amyloid fibrils. To accomplish this aim a dual expression system in baculovirus coexpressing normal TTR and variant TIR has been developed. These studies are directed at developing methods to prevent amyloid formation from variant TTR proteins and, thereby providing therapeutic options for a disease which at the present time has no specific therapy other than liver transplantation.

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- **Project Title: PERIPHERAL AND CENTRAL POSTURAL DISORDERS IN THE ELDERLY**

  Principal Investigator & Institution: Horak, Fay B.; Senior Scientist and Professor; None; Oregon Health & Science University Portland, or 972393098

  Timing: Fiscal Year 2001; Project Start 30-SEP-1989; Project End 31-MAR-2004

  Summary: (adapted from Investigator's abstract) The long-term goal of this research is to understand the neurophysiological basis for central and peripheral neurological disorders of postural control in order to provide a scientific basis for the evaluation and rehabilitation of balance disorders in the elderly. The first specific aim is to investigate the extent to which compensatory stepping is controlled in a similar way to step initiation by (1) testing the hypothesis that disorders of voluntary step initiation in 10 Parkinson's patients, 10 healthy young and 10 healthy elderly controls are similar to other disorders in stepping for balance correction (Experiment 1), and (2) determining the effect that a cognitive task has on voluntary step initiation, compensatory stepping, and feet in-place responses in 10 Parkinson patients ON and OFF levodopa and 10 healthy elderly controls (Experiment 2). The second aim investigates the effects of foot placement in stance on postural stability to perturbations in multiple directions. The hypothesis will be tested that 10 Parkinson, 10 cerebellar and 20 healthy elderly controls will not differ in their responses to such perturbations when standing with narrow, wide and diagonal foot placements (Experiment 3). Finally, the third aim is to determine how a cane is used for stability in stance and during surface perturbations. The hypothesis will be tested that a cane can be used to stabilize sway in stance, to modify and trigger automatic postural responses in patients with 10 **peripheral neuropathy** patients and up to 30 healthy controls, but not in 10 Parkinson's patients (Experiment 4). A better understanding of adaptive postural behaviors such as protective stepping, alterations in foot placement in stance, and use of a cane will provide the scientific rationale for improving balance retraining programs for both neurological patients and for elderly with subclinical disorders affecting balance.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: PERIPHERAL NEUROPATHY**

  Principal Investigator & Institution: Olney, Richard K.; Northern California Institute Res & Educ San Francisco, Ca 941211545

  Timing: Fiscal Year 2001

  Summary: Peripheral neuropathy is a frequent cause of HIV morbidity. Chronic heavy alcohol use, which itself is one of the two most prevalent causes of **peripheral neuropathy,** is common in populations at high risk for HIV infection. Chronic heavy alcohol use may effect the Peripheral Nervous System (PNS) morbidity of HIV infection by accelerating the development of immunodeficiency (via biological effects or via effects on treatment seeking and treatment adherence behavior), through interactions between toxic effects or through nutritional deficiency. This project will determine the effects ( and mechanisms underlying these effects) of chronic heavy alcohol use on clinical and functional measures of the Peripheral Nervous System (PNS) morbidity of HIV disease in a 2-year longitudinal study of HIV+ and HIV- chronic heavy drinkers (HIV+HD) and light/non-drinkers (HIV+ L/ND). The Project will: (1) determine whether HIV+ HDs have greater PNS morbidity at baseline than HIV+ L/NDs, (2) determine whether they have a more rapid rate of progression of PNS morbidity than HIV+ L/NDs, (3) determine whether the effects of chronic heavy alcohol use and HIV infection of PNS morbidity at baseline and over the follow-up period are additive or exceed additive effects, and (4) test hypotheses concerning the mechanism(s) for interaction of chronic heavy alcohol use and HIV infection of PNS morbidity and its progression and on the impact of polyneuropathy on clinically important outcomes. Four groups will be studied: 120 HIV+ HDs, 120 HIV+ L/NDs, 60 HIV-HDs, and 60 HIV- L/NDs. PNS function will be measured by clinical exam, quantitative sensory testing, quantitative autonomic testing, and nerve conduction studies. Quantitative sensory deficits will be measured with thermal and vibratory detection thresholds. Quantitative autonomic testing will include heart rate variation to deep breathing and the Valsalva maneuver as well as postural blood pressure testing. Electrophysiological measures will include sensory and motor nerve conduction studies of bilateral lower and non-dominant upper limbs. The establishment of chronic heavy alcohol consumption as a significant co-factor in the pathogenesis of DSP would heighten awareness of health care providers and patients to the importance of this co-factor and would open new therapeutic windows.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: PERIPHERAL NEUROPATHY, SENSORIMOTOR FUNCTIONS & BALANCE**

  Principal Investigator & Institution: Richardson, James K.; Phys Med and Rehabilitation; University of Michigan at Ann Arbor 3003 South State, Room 1040 Ann Arbor, Mi 481091274

  Timing: Fiscal Year 2001; Project Start 01-JUN-2000; Project End 31-MAY-2005

  Summary: (From application). This application requests support for the applicant to receive the didactic training and practical research experience necessary for him to become an independent, patient-oriented investigator. During the first two years of the award didactic course work will predominate, and during the last three research will be the greater focus; however, there will be elements of didactic education and participation in research throughout the duration of an award. The main focus of the coursework will be in biostatistics, epidemiology, and experimental design. Other didactic work will be through attendance at seminars sponsored by the University of

Michigan Pepper Center and Institute of Gerontology, as well as appropriate basic science and clinical conferences in other departments. Research to be performed will be under the direction of James Ashton-Miller, who will function as the applicant's mentor. It has been observed that in older patients with even mild **peripheral neuropathy** (PN) the rate of falls is increased. Specific distal lower extremity afferent and efferent impairments in such patients which underlie their postural instability have also been identified. The proposed research in this application will investigate the efficacy of interventions to compensate for these impairments by means of two randomized, controlled studies. In the first, older adults will be randomized to receive touch of a vertical surface, a standard cane, or a health-related video. Outcomes will include ankle inversion/eversion proprioceptive thresholds and comfortable gait speed and errors on a challenging walking task (irregular surface, low light). In the second, older adults with PN will undergo a 12-week strengthening program specifically designed for them or a control regimen. Outcomes will include maximum voluntary strength of ankle inversion/eversion, comfortable gait speed and errors on the same challenging walking task, ability to recover from a lateral leans test, rate of ankle strength development, and unipedal stance time. Stratification of the subjects in the first group by the presence of carpal tunnel syndrome and testing the subjects in the second group at 3 and 12 weeks may give insight into the mechanisms responsible for improvement noted.

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- **Project Title: PHYSIOLOGY OF ATP RELEASE IN CHRONIC PAIN**

  Principal Investigator & Institution: Matsuka, Yoshizo; None; University of California Los Angeles 10920 Wilshire Blvd., Suite 1200 Los Angeles, Ca 90024

  Timing: Fiscal Year 2002; Project Start 01-APR-2002; Project End 31-MAR-2006

  Summary: (provided by applicant) Chronic inflammatory and neuropathic pain is a problem of considerable clinical relevance. Understanding the mechanisms underlying development and maintenance of chronic pain would be a major step towards rational treatment of such pain conditions. Considerable evidence links chronic pain of neuropathic origin with increased excitability and abnormal signal generation in primary afferent neurons within sensory ganglia. Chemically-mediated cross-excitation between neurons in sensory ganglia has been proposed as one major mechanism by which abnormal discharges can be generated in pathological pain states. However, the identity of the chemical mediator of cross-excitation is unknown. Adenosine triphosphate (ATP) is released within sensory ganglia following neuronal activation and was shown to activate receptors on somata of sensory neurons. The overall goal of this proposal is to directly test the hypothesis that ATP is the chemical mediator of cross-excitation and to determine how release of ATP changes in pathological pain states. The specific aims are to: 1) determine the involvement of released ATP in cross-excitation of neurons within sensory ganglia, 2) determine the changes in basal and stimulus-evoked ATP release after peripheral inflammation, 3) determine the changes in basal and evoked ATP release after induction of sciatic neuropathy, 4) compare ATP release from different types of isolated and labeled DRG neurons. Cross-depolarization evoked by peripheral nerve stimulation will be measured during intracellular recordings from neurons in dorsal root ganglia (DRG). ATP receptors on sensory neurons will be manipulated by application of selective agonists and antagonists to influence evoked cross-depolarization. ATP release will be measured by the luciferin-luciferase assay in DRG perfusates. ATP release from acutely isolated DRG neurons will be measured using detector patches. These studies will be carried out first under normal conditions and then compared to results obtained after induction of a) peripheral inflammation,

and b) **peripheral neuropathy** in rats. The acquired knowledge may lead to the development of novel therapeutics targeting abnormal excitability changes in sensory neurons.

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- **Project Title: PILOT--DEVELOP MTHFR NULL AND C677T POLYMORPHIC MICE**

  Principal Investigator & Institution: Kucherlapati, Raju M.; Professor; Harvard University (Sch of Public Hlth) Public Health Campus Boston, Ma 02460

  Timing: Fiscal Year 2003; Project Start 18-SEP-2003; Project End 31-AUG-2008

  Summary: Methylenetetrahydrofolate reductase (MTHFR) is a protein that is important in folate metabolism. Its enzymatic activity is to convert 5, 10-methylenetetrahydrofolate to 5'-methyl tetrahydrofolate, which in turn is important in the methylation of homocysteine to methionine. Several variants and mutations in the gene for MTHFR have been described. Moderate or severe deficiencies of this enzyme lead to a number of disorders including hyperhomocystenuria and homocystenuria. The clinical outcome of the deficiency include **peripheral neuropathy,** developmental delay, hypotonia and seizures [1]. Mild forms of the reduced MTHFR activity are present in high frequencies in the general population. These variant forms of these enzymes lead to mild homocystinuria. High level of homocysteine is a risk factor for arterial disease [2-4]. The genes for human and mouse MTHFR have been isolated and characterized [4-7]. The human gene encodes a protein 656 amino acids in length and the mouse gene encodes a 654 aa protein. There is a high level of conservation between the human and mouse genes. At the amino acid level, the two proteins are 90% identical [5]. The exon-intron organization of the two genes is also identical. Both genes have 11 exons. Although several different size transcripts have been described [6, 7], all of them encode the identical protein. Several variants of the human MTHFR gene have been described. Of these, the C677T variant that converts an alanine codon to valine is the most studied. This is a very common polymorphism and has an allele frequency of approximately 35% in the North American population. The amino acid change leads to a thermolabile enzyme that causes a predisposition of homocystenuria when folate levels are low [4, 8, 9]. In this developmental project, we propose to make mice that have a null allele of the Mthfr gene and a second mouse that carries the homologous C677T variation. Based on the high level of identity between the two proteins and the complete conservation of the 10 amino acids on either side of the variation in the mouse and human genes suggests that the mouse will truly mimic the functional aspects of the C677T polymorphism in humans. Availability of these mice would help us in better defining the role of MTHFR and C677T variant on folate metabolism and how these genetic changes would affect colon cancer susceptibility under different nutritional folate levels. The steps that are involved in generating the mice are as follows: 1. Isolation of a mouse BAC from the 129/SvEvTac strain genomic library, 2. Modification of the gene, 3. Transfection of mouse ES cells with the gene modification construct and screening the colonies for the desired modification, 4. Injection of the modified ES cells into blastocysts to generate chimeras and 5. Mate the chimeras for germ-line transmission of the modified allele.

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- **Project Title: POSTTRANSLATIONAL PROCESSING BY ZMPSTE24 AND LAMINOPATHY**

  Principal Investigator & Institution: Ng, Jennifer K.; J. David Gladstone Institutes 365 Vermont St San Francisco, Ca 94103

Timing: Fiscal Year 2003; Project Start 26-MAR-2004

Summary: (provided by applicant): The proteins of the nuclear lamina have generated enormous interest because missense mutations in LMNA (the gene for prelamin A, which encodes both lamin A and lamin C) cause a host of diseases, including Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy, Charcot-Marie-Tooth type II **peripheral neuropathy,** and Hutchinson-Gilford progeria syndrome. Prelamin A, the precursor to mature lamin A, undergoes a series of posttranslational modifications, including the covalent attachment of a lipid to the protein, proteolytic clipping of the protein, and methylation of the protein. These post-translational modifications are important both to the targeting of the lamins to the nuclear envelope and to their function. The laboratory of my mentor, Dr. Stephen G. Young, recently identified an endoprotease, Zmpste24, that is required for the maturation of prelamin A to lamin A. Interestingly, Zmpste24-deficient mice develop a muscle weakness phenotype I strikingly similar to that observed in mice lacking lamin A/C. A key objective of my application is to define the pathological and molecular underpinnings of the possible muscular dystrophy, **peripheral neuropathy** and progeria phenotype in Zmpste24-deficient mice, as well as compare them to mice harboring mutant Lmna alleles. Finally, I will investigate the consequences of defective posttranslational processing of lamin A on a cellular level in order to elucidate the biochemical role of Zmpste24 in prelamin A processing.

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- **Project Title: PREGABALIN:SAFETY IN PATIENTS W/ PAINFUL DIABETIC PERIPHERAL NEUROPAT**

  Principal Investigator & Institution: Granda-Ayala, Ramona; Tulane University of Louisiana New Orleans, La New Orleans, La 70112

  Timing: Fiscal Year 2001

  Summary: Diabetic **peripheral neuropathy** is associated with several clinical entities, including diffuse neuropathy and focal neuropathy. Resistance to treatment with simple analgesics is a characteristic feature in painful diabetic neuropathy. There is a need for new effective drugs that can relieve the painful symptoms with minimal impact on the patient's diabetes control. Drugs such as non-narcotic analgesics, tricyclic antidepressants, anticonvulsants such as phenytoin, phenothiazine, antiarrhythmics, NSAIDs, and opiates have been used to treat painful neuropathy, with little success. Pregabalin has been shown to be effective in the treatment of diabetic **peripheral neuropathy.** In this study, pregabalin is being evaluated with the objective of providing another therapeutic option in the treatment of painful diabetic neuropathy.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: PROSAPOSIN AND PROSAPTIDES IN DIABETIC NEUROPATHY**

  Principal Investigator & Institution: Calcutt, Nigel A.; Associate Professor; Pathology; University of California San Diego 9500 Gilman Dr, Dept. 0934 La Jolla, Ca 92093

  Timing: Fiscal Year 2001; Project Start 30-SEP-1999; Project End 31-AUG-2003

  Summary: Diabetic **peripheral neuropathy** may be indicated by sensory disorders including spontaneous pain, hyperalgesia or allodynia, by slowed sensory and motor nerve conduction velocities or by structural pathology. Diabetic rats also develop sensory, electrophysiologic and subtle structural disorders. This supports their use as a model of the early stages of hyperglycemia-induced peripheral nerve disorders in the absence of overt structural pathology and allows study of both the etiologic mechanisms

linking hyperglycemia to nerve dysfunction and also development of potential therapeutic agents. Recent evidence suggest that peripheral nerve requires ongoing neurotrophic support and that hyperalglycemia disrupts this. Providing exogenous neurotrophic support that either replaces or supercedes diminished endogenous support mechanisms has been proposed as a therapeutic strategy for treating diabetic neuropathy. Prosaposin is the precursor for intracellular saposins but is also secreted in an unprocessed form which has neurotrophic properties. These neurotrophic properties are shared by prosaposin mimetics, small peptides derived from the prosaposin molecule that lack the other properties of saposins. Our preliminary data suggest that prosaposin mimetics called prosaptides prevent or attenuate electrophysiologic, biochemical and structural disorders in the peripheral nerve of diabetic rats, encompassing indices of both sensory and motor function in both large and small fibers. This broad spectrum of efficacy is beneficial for a potential therapeutic because diabetes affects all divisions of the peripheral nervous system. Prosaptides also rapidly ameliorate hyperalgesia in diabetic rats, suggesting a second action distinct from the neurotrophic properties and which may have additional therapeutic benefits to those diabetic patients who develop painful diabetic neuropathy. We propose to establish the therapeutic profiles of prosaptides for treating electrophysiologic and structural disorders of peripheral nerve in diabetic rats that are associated with developing neuropathy and also for treating disorders that reflect pain states. We will also correlate the therapeutic actions of prosaptides with effects on neurochemical abnormalities present in diabetic rats, including investigation of the effect of diabetes on endogenous prosaposin production. The goal is to establish prosaptides as novel therapeutic agents for treating diabetic neuropathy and to provide mechanistic explanations for why hyperglycemia causes nerve disorders.

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- **Project Title: RESTORING DIABETIC TACTILE SENSE WITH MECHANICAL NOISE**

  Principal Investigator & Institution: Harry, Jason D.; Afferent Corporation Box 160, 3 Davol Sq, Ste C200 Providence, Ri 02903

  Timing: Fiscal Year 2001; Project Start 30-SEP-2001; Project End 31-MAR-2003

  Summary: Stochastic resonance (SR) is a counterintuitive phenomenon in which slight amounts of noise imparted to a system actually increase its sensitivity to weak stimuli. SR has been shown to produce a demonstrable effect in human sensory cells. In both healthy young and clinical subjects-elderly, diabetics, and stroke sufferers-a notable increase in tactile and proprioceptive sensitivity is seen when electrical or mechanical noise is presented at the site of the stimulus. Dysfunction in the tactile system in diabetics is known to have significant clinical sequelae including gait abnormalities, propensity to fall, and foot ulcers. Diabetic **peripheral neuropathy,** with its complications, costs the U.S. healthcare system many billions of dollars annually. The goal of the proposed research is to advance early laboratory results toward a therapeutic device for enhancing the tactile sense in diabetic patients. The work will demonstrate the ability of mechanical stimulation to improve sensitivity using two metrics. First, we will determine the magnitude of the SR benefit in diabetics using standard neurological examinations, specifically the Semmes-Weinstein and vibration perception threshold tests. Second, we will explore the functional benefit of mechanical stimulation in stance and sway experiments. Both experiments will give a measure of true functional benefit. PROPOSED COMMERCIAL APPLICATIONS: If successful, the proposed research will lead to medical devices that improve tactile sensitivity in people who suffer from

diabetic **peripheral neuropathy.** This would improve quality of life for these individuals while reducing the costs of caring for them. Additional medical applications include use of technology in stroke, aging, and rehabilitation medicine.

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- **Project Title: ROLE OF LIF AND NGF IN INFLAMMATION AND CHRONIC PAIN**

  Principal Investigator & Institution: Hulsebosch, Claire E.; Professor; University of Texas Medical Br Galveston 301 University Blvd Galveston, Tx 77555

  Timing: Fiscal Year 2001; Project Start 01-FEB-1974; Project End 31-JUL-2006

  Summary: This project addresses the regulation of neuropeptide expression in chronic pain that appears following spinal cord injury. Such pain is often a severe affliction for the victim. A model established in our laboratories to investigate the pain that follows spinal cord injury will be utilized. In this model, pain-like behaviors that appear following hemisection of the rt spinal cord are assessed. The model reproduces the salient features of post spinal cord injury in humans. Our central hypothesis is that expression of the cytokine leukemia inhibitor factor (LIF) counteracts the development of chronic pain following spinal cord injury by increasing the expression of the neuropeptide galanin and decreasing the expression of the peptides nerve growth factor (NGF), substance and calcitonin gene related peptide. This hypothesis includes a sub-hypothesis that LIF acts on the synthesis of the latter peptides by reducing the biosynthesis of NGF. Existing evidence suggests that increased LIF reduces manifestations of pain in **peripheral neuropathy** and inflammation models by altering the production of neuropeptide inter cellular messengers. However, since this is unaddressed for the pain that develops following spinal cord injury, the biosynthesis of all of the above peptides and their effects on pain-like behaviors following spinal cord injury will be characterized. Time courses of effects of injury on peptide biosynthesis will be determined by analyzing peptides in tissue from the area of injury by ELISA or RIA assays and by immunocytochemistry. Roles of these peptides in pain expression will be tested by blocking their actions during times of increased expression or adding them when their expression is decreased, together with measuring pain-like behaviors in the experimental animals. The actions of LIF or NGF will be manipulated so as to increase peptide synthesis and then the action of that peptide will be blocked to establish whether modulation of peptide biosynthesis by LIF and NGF influences pain-like behaviors. Effects of LIF of inflammation and associated pain will also be characterized. Insights from this work will aid in developing treatments for pain that appears following spinal cord injury, currently a clinically intractable problem.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: SKIN INTERFACE FRICTION TRANSDUCER**

  Principal Investigator & Institution: Schoess, Jeffrey N.; Korosensor.Com, Inc. 3421 50Th St, Ne Buffalo, Mn 55313

  Timing: Fiscal Year 2003; Project Start 15-AUG-2003; Project End 30-JUN-2004

  Summary: (provided by applicant): Korosensor proposes to develop a skin interface friction transducer (SIFT) to prevent skin breakdown in diabetic mellitus patients, which can lead to foot ulceration and lower extremity amputation. The risk of lower extremity amputation is 15 to 46 times higher in diabetics than persons without diabetic mellitus, with the vast majority of diabetic foot complications resulting in amputation due to formation of skin ulcers. Many of these patients experience loss or complete absence of protective skin sensation (i.e. excessive rubbing, redness and swelling, excessive

pressure) due to **peripheral neuropathy.** When a lack of sensation is coupled with abnormal pressure, a foot ulcer can form. Many of these ulcerous problems can be prevented if artificial sensing is developed to complement a patient's sensory response to alert the patient the potential exists for skin breakdown and damage. The proposed Phase I project will establish the technical and commercial feasibility of developing a skin interface friction transducer that can detect the 'stick-slip' condition in diabetic patients. A low-profile polymer sensor pad incorporating SIFT will be fabricated with several ridge elements and inserted into footwear. A series of ridges will be replicated in the sensor pad to emulate the epidermal features of human skin. Each element will be designed to sense dual-use forces, the normal (i.e. perpendicular) force, FN and tangential forces (FT) at the foot surface. The coefficient of friction will be determined. The sensor pad will be designed to promote patient self-care, informing the patient, through wireless RF telemetry of diabetic foot condition.

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- **Project Title: SPATIAL PROPERTIES OF CUTANEOUS TEMPERATURE SENSITIVITY**

  Principal Investigator & Institution: Green, Barry G.; Fellow; John B. Pierce Laboratory, Inc. 290 Congress Ave New Haven, Ct 06519

  Timing: Fiscal Year 2001; Project Start 02-MAR-1999; Project End 30-NOV-2002

  Summary: (adapted from the applicant's abstract) The PI recently discovered that areas of skin can be found that lack sensitivity to warmth. These surprisingly large (5 sq.cm.), warmth-insensitive fields (WIFs), which are indifferent to heating below 41C, contradict the view that macroscopic warm stimuli can be sensed everywhere on the skin and imply that cutaneous innervation by low-threshold warm fibers can be remarkably sparse and irregular. The PI states that the discovery of WIFs illustrates the need for a reanalysis of the spatial distribution of warmth sensitivity using modern methods of psychophysical measurement and temperature control. Accordingly, the first goal of his project is to study the topography of warmth sensitivity in different body regions and across individuals, and to determine how differences in the spatial density and distribution of warmth may contribute to regional and individual differences in perception of macroscopic stimuli. The second goal of this project is to investigate the extent to which warmth topography may change over time. Early maps of punctate thermal sensitivity were inherently variable, and preliminary data suggest that over periods of weeks or months, sensitivity can develop within previously identified WIFs. The third goal of his project is to take advantage of the extraordinary opportunities WIFs provide to study heat nociception and cold perception directly, independent of afferent activity in the warmth sense. The PI proposes experiments that will use WIFs to investigate basic psychophysical properties of these two systems and to address long-standing questions about the possible contribution of the low-threshold warmth system to the perception of cold, heat, and heat pain. Overall, the proposed studies should yield novel psychophysical data that have the potential to change current thinking about the spatial organization and functional characteristics of human thermal sensitivity. In addition, studies of regional and individual differences in warmth topography and of the contribution of the warmth system to heat and heat pain will provide information essential to the use and interpretation of thermal sensitivity in clinical assessments of **peripheral neuropathy.**

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: SPONTANEOUS AUTOIMMUNE MODEL OF PERIPHERAL NEUROPATHY**

  Principal Investigator & Institution: Bluestone, Jeffrey A.; Professor and Director; Diabetes Center; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 94122

  Timing: Fiscal Year 2002; Project Start 15-DEC-2001; Project End 30-NOV-2006

  Summary: (provided by investigator): Guillain-Barre Syndrome (GBS) and Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) are autoimmune diseases characterized by inflammatory demyelinating lesions of the peripheral nervous system that cause devastating neurological deficits and paralysis. We have developed the first model of spontaneous autoimmune disease of the peripheral nervous system, called Spontaneous Autoimmune **Peripheral Polyneuropathy** (SAPP). NOD mice deficient in the co-stimulatory molecule B7-2 exhibit a progressive and generalized limb paralysis associated with severe demyelination and axonal damage due to massive inflammation of the peripheral nervous system. Adoptive transfer experiments showed that the disease is mediated, at least in part, by CD4+ T cells. The course of the disease and its pathophysiological features are strikingly similar to human GBS and CIDP. SAPP is observed in mice of the autoimmune-prone NOD background, which has been widely recognized as a valuable animal model of autoimmunity in humans. Furthermore, B7-2-deficient NOD mice do not develop diabetes. Thus, this animal model will provide insight into the influence of the co-stimulatory milieu on the polarization of autoimmunity towards different tissues and the development of distinct diseases in individuals presenting a general susceptibility to autoimmunity. The following specific aims are proposed to study this disease: Specific aim #1: To determine the antigen(s) targeted by autoreactive T cells in the peripheral nerves. Specific aim #2: To understand the influence of B7 costimulation on the polarization of autoimmunity in nod mice. Specific aim #3: To determine the immunopathology of SAPP, particularly the cell subsets and the effector mechanisms involved in the disease. Specific aim #4: To analyze the genetic control of SAPP. We propose to study the hypothesis that SAPP shares a subset of immunological and genetic attributes similar to those associated with the other autoimmune syndromes in the NOD strain. Our results will allow us to define genetic and immunological characteristics that determine the general susceptibility of individuals to autoimmunity and identify distinct mechanisms that lead to spontaneous destructive immune response in the nervous system versus the pancreas.

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- **Project Title: STRUCTURE/FUNCTION ANALYSIS OF LOW PL CONNEXIN ISOFORMS**

  Principal Investigator & Institution: Hertzberg, Elliot L.; Professor; Neuroscience; Yeshiva University 500 W 185Th St New York, Ny 10033

  Timing: Fiscal Year 2002; Project Start 01-APR-2002; Project End 31-MAR-2004

  Summary: (provided by applicant): Gap junctions are assemblages of cell-cell channels occurring in regions of cell contact. These channels permit direct intercellular communication by passive diffusion of low molecular weight hydrophilic molecules, including calcium, cyclic nucleotides, inositol phosphates and other signaling molecules. Several gap junction proteins, termed connexins, serve prominent roles in the nervous system. Among these, Connexin43 (Cx43) is expressed at high levels in astrocytes where they provide a mechanism of spatial buffering of ions and exert a modulatory influence on neuronal activity. Mutations of Cx32, found in myelin, lead to a progressive

**peripheral neuropathy** termed X-linked Charcot-Marie-Tooth disease. Mutations in Cx26 underlie the most common forms of non-syndromic deafness. Interestingly, connexins are the only family of plasma membrane proteins that do not appear to be glycosylated. Preliminary studies of Cxs 43, 32 and 26 indicate that they are significantly more negatively charged than anticipated based upon their sequence and known covalent modifications. That these pI variants are indistinguishable by SDS-PAGE indicates that the molecular basis for acidic pI variants is of low molecular weight. The specific aims of this proposal are to (1) identify this modification and the altered amino acid residues and (2) determine its role in the assembly and functioning of gap junction channels. Our approach to determining the chemical basis of connexin will be biochemical, relying especially on mass spectrometry, and genetic engineering. The role of this modification will be assessed using pharmacology and site-direct mutagenesis. Identification of a low Mr anion covalently attached to connexins might provide the first target for pharmacological intervention in gap junction function. Knowledge of where charged residues exist will profoundly influence modeling studies of connexins and, likely, other membrane proteins, in which alterations of electrostatic interactions play a role in channel selectivity and gating. Many of the experiments will push experimental procedures for use in the study of membrane proteins. Establishing the basis of connexin charge alteration will introduce a new player in chemical modification of proteins and their properties.

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- **Project Title: SURAMIN W/ SEQUENTIAL DOXORUBICIN IN PATIENTS W/ ADVANCED SOLID TUMOR**

  Principal Investigator & Institution: Adjei, Alex A.; Mayo Clinic Rochester 200 1St St Sw Rochester, Mn 55905

  Timing: Fiscal Year 2001

  Summary: Suramin is a unique polyanionic compound which blocks a variety of growth factors involved in the proliferation of human tumors. Doxorubicin is an anthracycline antibiotic which interferes with DNA topoisomerase II. Based on preclinical data, suramin with sequential doxorubicin possess cytotoxic synergy in a number of tumor types including prostate and breast carcinomas. It is our hypothesis that suramin with sequential doxorubicin is a potent and effective antitumor treatment. We are undertaking a phase I trial of suramin with sequential doxorubicin in patients with solid tumors refractory to standard therapy or for whom there is no standard treatment. The objectives of the trial are: 1) to determine the MTD of 4 days of short infusion suramin followed by 1 dose of ADR (varying doses) repeated every 4 weeks, 2) to describe the toxicities of suramin with sequential ADR given on this schedule, 3) to assess the development of **peripheral neuropathy** in patients treated with suramin-ADR on this schedule, 4) to seek preliminary evidence of the antitumor effect of suramin with sequential ADR, 5) to determine the effect of suramin on total and free IGF-1, IGF-2, and IGFBPs, 6) the pharmacokinetic studies will be performed to explore relationships between pharmacokinetic parameters and potential neurotoxicity. Those parameters will include total dose, peak and trough concentrations, total AUC and time above a threshold concentration or AUC. The eligibility criteria are >18 years of age; unavailability of another more conventional form of therapy which offers a reasonable chance to cure, performance status 0-2, adequate organ function, life expectancy of >12 weeks, grade 2. Patients meeting the eligibility criteria will receive suramin intravenously on days 1-4 followed by a bolus infusion of doxorubicin done on day 5. Treatment will be repeated every 28 days up to a maximum of 3 cycles. The starting

dose of doxorubicin will be 20 mg/m2 on day 5 and will be escalated to 30, 45, and 60 mg/m2 in subsequent patient cohorts. The dose of suramin will be fixed, and is chosen to yield peak and through levels of 200 ug/ml and 150 ug/ml respectively. Dose-limiting toxicity is defined as that dose in which >2/3 or >2/6 patients experienced serum creatinine >2 times baseline or > 2 times institutional upper normal (whichever is highest) >grade 3 other nonhematologic or >grade 3 hematologic toxicities according to NCI CTC. The maximally tolerated dose is one dose level below that dose which causes dose-limiting toxicity. An exploratory analysis will be undertaken to relate the pharmacokinetic parameters of this treatment and clinical or hematologic toxicity.

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- **Project Title: SYMPTOMATIC TREATMENT OF PERIPHERAL NEUROPATHIES**

  Principal Investigator & Institution: Sui, Jinliang; Cambridge Neuroscience 333 Providence Hwy Norwood, Ma 02062

  Timing: Fiscal Year 2001; Project Start 30-SEP-1997; Project End 31-AUG-2002

  Summary: Our overall therapeutic goal is to develop a drug treatment that reduces suffering and improves quality of life for victims of **peripheral neuropathies** - a diverse group of neurological disorders with genetic, metabolic or toxic etiologies. Patients who suffer from **peripheral neuropathy** can experience loss of voluntary or involuntary motor function and a wide range of disordered sensations, including intense chronic pain. In **peripheral neuropathies,** demyelination of nerve axons is associated with loss of signal propagation that directly or indirectly causes the symptoms of the neuropathy. Exposure of specific voltage-gated potassium channels on nerve axons by demyelination creates a condition where the propagation of action potentials can be terminated by a "short circuit". Our mechanistic approach is to selectively block this specific class of voltage-gated potassium channels and restore axonal conduction in demyelinated peripheral nerves. In Phase I of the project, we successfully established the basic screening technologies, developed a focused chemical library of potassium channel blockers and identified lead molecules. In Phase II, we will study compounds from an expanded chemical library using in vitro assays and animal efficacy and safety "models" with the objective of selecting candidates for preclinical and clinical development. PROPOSED COMMERCIAL APPLICATION: **Peripheral neuropathies** afflict millions of people in the United States and tens of millions worldwide. For example, the NIDDK estimates that 16 million people in the US have diabetes and that 30-40% of diabetics have symptoms of **peripheral neuropathy.** In addition, certain drugs used in treating cancer cause an estimated 260,000 cases each year of **peripheral neuropathy** that can limit the use of the chemotherapeutic agents. There is no doubt that an effective drug treatment for the symptoms of **peripheral neuropathy** would have a substantial medical. societal and commercial impact.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: TEXAS REPOSITORY FOR AIDS NEUROPATHOGENESIS RESEARCH**

  Principal Investigator & Institution: Gelman, Benjamin B.; Professor; Pathology; University of Texas Medical Br Galveston 301 University Blvd Galveston, Tx 77555

  Timing: Fiscal Year 2003; Project Start 30-SEP-1998; Project End 31-MAY-2008

  Summary: (provided by the applicant): The National NeuroAIDS Tissue Consortium (NNTC) is a national repository for CNS and PNS specimens that opened the way for fundamental research on the mechanism and treatment of HIV-related neurocognitive

disease. The early phase of the project focused on forming the National Steering Committee to standardize the protocol Subjects were recruited, neurocognitive impairment was assessed, structured neurological examinations were performed, substance use was documented, and blood and CSF virologic status were determined. A quality assurance (QA) program was implemented to control for variability between sites, and a web-based database was established. A National Coordinating Office was established to process specimen requests, and to provide data to the community (www.hivbrainbanks.org). After 3 3/4 years, the NNTC recruited a cohort that produced about 165 well-characterized HIV-infected decedents who underwent autopsy. There are over 600 active subjects in the cohort likely to undergo autopsy in the future. Investigators can use these data to compare new discoveries with the clinical information that we have collected. The Texas HIV Brain Bank operates a website that offers vetted investigators additional options. Our repository responded effectively to over 91 % of all NNTC specimen requests. Much more neurochemical, molecular and morphological study of human CNS specimens needs to be performed on these resources. To continue building durable assets and serving the research community, we propose to continue operating the Texas Repository in a renewed NNTC project. We will follow to autopsy, over the next five years, 129 well-characterized HIV infected subjects in the Texas NNTC cohort. We will carry out a brain bank resource utilization program to address the scientific themes of our site. We will: 1) perform gene expression profiles on dorsal root ganglia from patients with **peripheral neuropathy** (DSP); 2) determine if a polymorphic TNF-a allele is over-represented in people with DSP and/or dementia; 3) isolate microglial cells from human autopsy brain, infect them with HIV-1, and distribute cells and media to the research community; 4) construct a linear multiple regression model of brain cell counts, including subspecies of mononuclear phagocytes, brain HIV loads, and neurochemical changes to determine their clinical relevancy in our cohort.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: THERAPEUTIC ANGIOGENESIS IN VASCULAR MEDICINE II**

  Principal Investigator & Institution: Isner, Jeffrey; Professor; St. Elizabeth's Medical Center of Boston 736 Cambridge St Boston, Ma 02135

  Timing: Fiscal Year 2001; Project Start 01-JAN-1995; Project End 31-JAN-2005

  Summary: Experiments performed in animal models have established that administration of angiogenic growth factors as recombinant proteins or by gene transfer promotes neovascularization of ischemic tissues. Preliminary investigations in patients with critical limb ischemia suggest that this strategy, termed therapeutic angiogenesis, may yield potential clinical benefit, including relief of rest pain and restoration of tissue integrity. Follow-up studies of these patients and preliminary animal studies suggest that therapeutic angiogenesis may also lead to recovery of nerve function in patients and animals with ischemic **peripheral neuropathy.** Accordingly, this Proposal has been designed to systematically investigate the impact of therapeutic angiogenesis on ischemic **peripheral neuropathy.** The proposed experiments have been designed to test specific hypotheses, organized according to three Specific Aims. Specific Aim 1 will determine the impact of therapeutic angiogenesis on ischemic **peripheral neuropathy,** using a rabbit model of hindlimb ischemia. These experiments will evaluate what has been considered to be a relatively endothelial cell (EC)-specific cytokine, vascular endothelial growth factor (VEGF), as well as more pleiotropic angiogenic growth factors. The impact of angiogenesis inhibitors on endogenous recovery of nerves injured due to ischemia will be investigated as well. Specific Aim 2 will employ animal models

with experimentally induced diabetes to determine the impact of angiogenic growth factors on **peripheral neuropathy,** with and without macrovascular insufficiency. The response of ischemic neuropathy to neurotrophins will also be investigated in these animal models. The third Specific Aim is to investigate the cellular basis for modulation of ischemic **peripheral neuropathy** by therapeutic angiogenesis. These experiments will determine whether the impact of VEGF on ischemic neuropathy is limited to indirect effects achieved by enhanced neovascularization, or whether VEGF may directly modulate non-vascular neural elements. The extent to which angiogenic growth factors and ischemia modulate expression of endogenous neurotrophins will be investigated as well. Finally, mechanisms responsible for peripheral nerve recovery in response to angiogenic cytokines will be studied for contribution of bone-marrow derived endothelial precursors to putative neovascularization of the vasa nervorum. The experiments outlined in this Proposal are anticipated to provide new insights into the fundamental relationship between vascular and peripheral nerve integrity, and suggest novel therapeutic strategies to address a clinical disorder that accounts for considerable morbidity.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: TRIAL OF LAMICTAL IN ADULT HIV PERIPHERAL NEUROPATHY**

  Principal Investigator & Institution: Mcarthur, Justin C.; Professor of Neurology; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2001

  Summary: The purpose of this study is to evaluate the efficacy and safety of lamotrigine for the treatment of pain in subjects with HIV-peripheral neuropathy. **Peripheral neuropathy** is a frequent late-stage complication of HIV infection. The most common form is a symmetric, predomininately sensory, distal polyneuropathy that affects 20-35% of patients with late-stage HIV infection. The clinical signs and symptoms of HIV **peripheral neuropathy** (HIV-PN) include pain, numbness, and burning sensations primarily in the feet. The cause of HIV-PN remains unknown. A number of medications have been used in the treatment of HIV-PN, including antidepressants, anticonvulsants, opiate and non-opiate analgesics and local anesthetics. All of these have variable and generally incomplete efficacy. Lamotrigine is an anticonvulsant with similar efficacy in maximal electroshock models to carbamazepine and phenytoin, both with proven benefit in the treatment of painful diabetic neuropathy. The proposed mechanism of action of lamotrigine is a blocking effect on voltage-sensitive sodium channels and inhibition of glutatmate and aspartate release. An excess of these excitotoxins may play a role in AIDS neuropathy. Anecdotal reports and published data from small, uncontrolled clinical trials suggest that lamotrigine may be an effective treatment for neuropathic pain. These results suggest a larger study is warranted.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: VEGF GENE TRANSFER FOR DIABETIC NEUROPATHY**

  Principal Investigator & Institution: Ropper, Allan H.; St. Elizabeth's Medical Center of Boston 736 Cambridge St Boston, Ma 02135

  Timing: Fiscal Year 2002; Project Start 01-SEP-2002; Project End 31-AUG-2006

  Summary: Among diabetics, **peripheral neuropathy** is common and ultimately accounts for significant morbidity. The ultimate consequence of such sensory deficits involving the lower extremities may be foot ulceration initiated by trauma that is inapparent to the pt. Such ulcerations often lead to lower extremity amputation, a complication that is 15

times higher in diabetic versus non-diabetic pts. Preliminary clinical studies have demonstrated improvement in signs and symptoms of sensory neuropathy in pts with lower extremity vascular occlusive disease following intramuscular injection of naked DNA encoding vascular endothelial growth factor (VEGF). To determine if such a strategy could be applied to diabetic pts, including those without evidence of large vessel occlusive disease, we investigated the hypothesis that experimental diabetic neuropathy results from destruction of the vasa nervorum and can be reversed by administration of an angiogenic growth factor. In two different animal models of diabetes, nerve blood flow and the number of vasa nervorum were found to be markedly attenuated resulting in severe **peripheral neuropathy.** In contrast, following VEGF gene transfer, vascular and blood flow in nerves of treated animals were similar to those of non-diabetic controls; constitutive over-expression of VEGF resulted in restoration of large and small fiber peripheral nerve function. These findings implicate microvascular disruption as the basis for diabetic neuropathy and suggest that angiogenic growth factors may constitution a novel treatment strategy for this pernicious disorder. Accordingly, we now seek to address the following two specific aims: 1. Specific Aim #1: To evaluate the safety and impact of VEGF gene transfer on sensory neuropathy in pts with diabetes and associated lower extremity macrovascular disease; and 2. Specific Aim #2: To evaluate the safety and impact of VEGF gene transfer on sensory neuropathy in pts with diabetes without lower extremity macrovascular disease.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: VIBROMETER FOR ANIMAL TESTING**

  Principal Investigator & Institution: Tuckett, Robert P.; Neuroscience Research 2381 Sheridan Rd Salt Lake City, Ut 84108

  Timing: Fiscal Year 2001; Project Start 01-JUL-2001; Project End 30-JUN-2003

  Summary: (From the applicant's Abstract) One traditional quantitative animal assay for **peripheral neuropathy** involves measuring the animal's behavioral threshold to noxious thermal stimulation. A limitation of this approach is that thermally activated sensory populations are for the most part unmyelinated; hence, correlation with direct electrophysiological recording is extremely difficult and time-consuming. Alternatively, monofilament testing with hand-held probes provides a ranking of sensory threshold in large mechanosensory axons, which are relatively easy to record and identify histologically. In addition, recent evidence supports the concept that mechanoreceptor sensory pathways are involved in signaling chronic pain. The development of a stimulation procedure that is more quantitative than monofilament testing would be of benefit in behavioral studies of peripheral sensory neuropathy (e.g., diabetes, burn injury, compression, and AIDS), and development of new drugs for treatment of chronic pain, as well as basic investigations in genetics and neurobiology. Neuroscience research proposes the commercial development model system with standard procedures and instrumentation to quantify mechanosensory-related neuropathy in animal models. Phase I will test system feasibility in animal models of **peripheral neuropathy** that exhibit mechanical allodynia (diminished threshold to mechanically induced pain). PROPOSED COMMERCIAL APPLICATION: Markets for instrumentation to quantify animal **peripheral neuropathy** include numerous basic and applied research laboratories; e.g., those involved in genetic, neuroscience, and neurobiological studies of peripheral neural development and function; pharmaceutical companies screening for compounds to treat acute and chromic pain, as well as neurotoxicity; and laboratories

studying **peripheral neuropathy** (e.g., AIDS, diabetic, compression, chemical neurotoxicology).

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: XALD--ROLE OF VERY LONG CHAIN FATTY ACYL COA SYNTHETASES**

  Principal Investigator & Institution: Watkins, Paul A.; Associate Professor; Kennedy Krieger Research Institute, Inc. Baltimore, Md 21205

  Timing: Fiscal Year 2001; Project Start 01-FEB-1999; Project End 31-JAN-2003

  Summary: X-linked adrenoleukodystrophy (XALD) is a progressive neurodegenerative disorder with two main clinical phenotypes, a rapidly fatal, childhood- onset cerebral form and a milder, slowly progressive adult-onset **peripheral neuropathy.** Biochemically, decreased very long-chain fatty acid (VLCFA) activation by very long-chain acyl-CoA synthetase (VLCS) in peroxisomes results in impaired VLCFA beta-oxidation and subsequent elevation of tissue VLCFA levels. ALDP, the product of the gene defective in XALD, resembles ATP-binding cassette transmembrane transporter proteins and is not a VLCS. We hypothesize that disruption of a VLCS/ALDP interaction is responsible for loss of VLCS activity, and thus XALD. We have identified a new family of proteins that includes VLCS, and have cloned six human, mouse and yeast VLCS genes and homologs. One objective of this proposal is to identify the requirements and components of the peroxisomal VLCFA activation system and to determine how this process is disrupted in XALD. A second objective is to characterize the members of this newly described protein family with respect to both XALD and VLCFA metabolism. To accomplish this, VLCFA activation will be studied in yeast and mouse model systems. The yeast VLCS (Fatlp) will be characterized and other enzymes with VLCS activity will be identified. Gene disruption strategies will be used both to elucidate the components of VLCFA activation in yeast and to create a vehicle for expression of homologous mammalian genes. The remaining mouse and human VLCSs will be cloned and their gene products characterized. The mouse model of XALD created by targeted gene disruption will then be used to investigate the effects of ALDP absence on VLCS activity, tissue expression, and subcellular distribution. Furthermore, to determine whether VLCS tissue expression could affect phenotypic expression in XALD, the various mouse and human VLCS genes will be mapped and their map positions compared to emerging chromosomal locations of candidate XALD modifier genes.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ZENARESTAT IN DIABETIC NEUROPATHY**

  Principal Investigator & Institution: Fonseca, Vivian A.; Professor; Tulane University of Louisiana New Orleans, La New Orleans, La 70112

  Timing: Fiscal Year 2001

  Summary: One of the many complications associated with diabetes is **peripheral neuropathy,** which may affect up to 90% of diabetic patients with about 25% having clinical signs or symptoms. Diabetic **peripheral neuropathy** is defined as nerve damage attributable solely to diabetes mellitus; it can be either clinically evident or subclinical in nature and may involve the somatic and/or autoimmune nervous systems. The **peripheral neuropathies** are generally progressive and usually irreversible and often progress to a severe loss of sensation in the lower extremities, a condition that leads to an increased incidence of foot ulcers, infections, and amputations. The purpose of this

study is to determine if CI-1014 (zenarestat), an aldose reductase inhibitor, can reverse, stabilize, or slow the progression of diabetic neuropathy relative to placebo and to assess the safety of CI-1014.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

## E-Journals: PubMed Central[3]

PubMed Central (PMC) is a digital archive of life sciences journal literature developed and managed by the National Center for Biotechnology Information (NCBI) at the U.S. National Library of Medicine (NLM).[4] Access to this growing archive of e-journals is free and unrestricted.[5] To search, go to **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Pmc**, and type "peripheral neuropathy" (or synonyms) into the search box. This search gives you access to full-text articles. The following is a sample of items found for peripheral neuropathy in the PubMed Central database:

- **Does a neuroimmune interaction contribute to the genesis of painful peripheral neuropathies?** by Bennett GJ.; 1999 Jul 6;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=33611

## The National Library of Medicine: PubMed

One of the quickest and most comprehensive ways to find academic studies in both English and other languages is to use PubMed, maintained by the National Library of Medicine.[6] The advantage of PubMed over previously mentioned sources is that it covers a greater number of domestic and foreign references. It is also free to use. If the publisher has a Web site that offers full text of its journals, PubMed will provide links to that site, as well as to sites offering other related data. User registration, a subscription fee, or some other type of fee may be required to access the full text of articles in some journals.

To generate your own bibliography of studies dealing with peripheral neuropathy, simply go to the PubMed Web site at **http://www.ncbi.nlm.nih.gov/pubmed**. Type "peripheral neuropathy" (or synonyms) into the search box, and click "Go." The following is the type of output you can expect from PubMed for peripheral neuropathy (hyperlinks lead to article summaries):

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[3] Adapted from the National Library of Medicine: **http://www.pubmedcentral.nih.gov/about/intro.html**.

[4] With PubMed Central, NCBI is taking the lead in preservation and maintenance of open access to electronic literature, just as NLM has done for decades with printed biomedical literature. PubMed Central aims to become a world-class library of the digital age.

[5] The value of PubMed Central, in addition to its role as an archive, lies in the availability of data from diverse sources stored in a common format in a single repository. Many journals already have online publishing operations, and there is a growing tendency to publish material online only, to the exclusion of print.

[6] PubMed was developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM) at the National Institutes of Health (NIH). The PubMed database was developed in conjunction with publishers of biomedical literature as a search tool for accessing literature citations and linking to full-text journal articles at Web sites of participating publishers. Publishers that participate in PubMed supply NLM with their citations electronically prior to or at the time of publication.

- **A clinical study on treatment of diabetic peripheral neuropathy with tang zhi min capsules.**
  Author(s): Ren H.
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  Author(s): Pena JM, Fernandez E, Borras M, Montoliu J.
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  Author(s): Richardson JK, Sandman D, Vela S.
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  Author(s): Lefrandt JD, Bosma E, Oomen PH, Hoeven JH, Roon AM, Smit AJ, Hoogenberg K.
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  Author(s): Richardson JK.
  Source: Archives of Physical Medicine and Rehabilitation. 2002 November; 83(11): 1553-8.
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  Source: Journal of Clinical Neuroscience : Official Journal of the Neurosurgical Society of Australasia. 2001 November; 8(6): 520-4.
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  Author(s): Mezin P, Brion JP, Vermont J, Micoud M, Stoebner P.
  Source: Ultrastructural Pathology. 1991 November-December; 15(6): 593-602.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1665928&dopt=Abstract

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  Author(s): Hurvitz EA, Richardson JK, Werner RA.
  Source: Archives of Physical Medicine and Rehabilitation. 2001 February; 82(2): 198-204.
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  Source: Clinical Journal of Oncology Nursing. 2003 May-June; 7(3): 299-303. Review.
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  Author(s): Galantino ML, Eke-Okoro ST, Findley TW, Condoluci D.
  Source: Journal of Alternative and Complementary Medicine (New York, N.Y.). 1999 April; 5(2): 135-42.
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  Author(s): Davis JL.
  Source: Diabetes Care. 2000 October; 23(10): 1594-5.
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  Author(s): Andrews TR, Colon-Otero G, Calamia KT, Menke DM, Boylan KB, Kyle RA.
  Source: Mayo Clinic Proceedings. 2002 December; 77(12): 1287-90.
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  Author(s): Freeman RW, Bleecker ML, Comstock GW, Brookmeyer RS.
  Source: American Journal of Epidemiology. 1985 February; 121(2): 291-300.
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  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=199947&dopt=Abstract

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  Author(s): De Martino L, Sampaolo S, Tucci C, Ambrosone L, Budillon A, Migliaresi S, Di Iorio G.
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  Source: Metab Pediatr Syst Ophthalmol. 1986; 9(2-4): 85-7.
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  Author(s): Gimsing P, Melgaard B, Andersen K, Vilstrup H, Hippe E.
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  Author(s): Dellagi K, Dupouey P, Brouet JC, Billecocq A, Gomez D, Clauvel JP, Seligmann M.
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  Author(s): Vital C, Deminiere C, Bourgouin B, Lagueny A, David B, Loiseau P.
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  Author(s): Wang CR, Chiu HC, Hsieh HC, Hsieh RP, Wu YC, Chuang CY.
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  Source: Journal of Neurology, Neurosurgery, and Psychiatry. 1992 January; 55(1): 56-9.
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  Author(s): Umehara F, Abe M, Nakagawa M, Izumo S, Arimura K, Matsumuro K, Osame M.
  Source: Neurology. 1993 June; 43(6): 1252-4.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8170578&dopt=Abstract

- **What is it? Case 1, 1992: progressive gait deterioration, peripheral neuropathy, optic atrophy, bradykinesia, and dystonia in a young girl.**
  Author(s): Russman BS, Lang AE, Fahn S, Greene P, Grunnet ML.
  Source: Movement Disorders : Official Journal of the Movement Disorder Society. 1992 October; 7(4): 373-9.
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# CHAPTER 2. NUTRITION AND PERIPHERAL NEUROPATHY

## Overview

In this chapter, we will show you how to find studies dedicated specifically to nutrition and peripheral neuropathy.

## Finding Nutrition Studies on Peripheral Neuropathy

The National Institutes of Health's Office of Dietary Supplements (ODS) offers a searchable bibliographic database called the IBIDS (International Bibliographic Information on Dietary Supplements; National Institutes of Health, Building 31, Room 1B29, 31 Center Drive, MSC 2086, Bethesda, Maryland 20892-2086, Tel: 301-435-2920, Fax: 301-480-1845, E-mail: ods@nih.gov). The IBIDS contains over 460,000 scientific citations and summaries about dietary supplements and nutrition as well as references to published international, scientific literature on dietary supplements such as vitamins, minerals, and botanicals.[7] The IBIDS includes references and citations to both human and animal research studies.

As a service of the ODS, access to the IBIDS database is available free of charge at the following Web address: **http://ods.od.nih.gov/databases/ibids.html**. After entering the search area, you have three choices: (1) IBIDS Consumer Database, (2) Full IBIDS Database, or (3) Peer Reviewed Citations Only.

Now that you have selected a database, click on the "Advanced" tab. An advanced search allows you to retrieve up to 100 fully explained references in a comprehensive format. Type "peripheral neuropathy" (or synonyms) into the search box, and click "Go." To narrow the search, you can also select the "Title" field.

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[7] Adapted from **http://ods.od.nih.gov**. IBIDS is produced by the Office of Dietary Supplements (ODS) at the National Institutes of Health to assist the public, healthcare providers, educators, and researchers in locating credible, scientific information on dietary supplements. IBIDS was developed and will be maintained through an interagency partnership with the Food and Nutrition Information Center of the National Agricultural Library, U.S. Department of Agriculture.

The following is a typical result when searching for recently indexed consumer information on peripheral neuropathy:

- **Food shortages and an epidemic of optic and peripheral neuropathy in Cuba.**
  Author(s): School of Nutrition and a Research Scientist, USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA 02111.
  Source: Tucker, K Hedges, T R Nutr-Revolume 1993 December; 51(12): 349-57 0029-6643

- **Impact of peripheral neuropathy on bone density in patients with type 1 diabetes.**
  Author(s): Medical Department C, Roskilde County Hospital Koge, Denmark. mariannerix@hotmail.com
  Source: Rix, M Andreassen, H Eskildsen, P Diabetes-Care. 1999 May; 22(5): 827-31 0149-5992

- **Lack of effect of clonidine and pentoxifylline in short-term therapy of diabetic peripheral neuropathy.**
  Author(s): Department of Medicine, Yale University School of Medicine, New Haven, Connecticut.
  Source: Cohen, K L Lucibello, F E Chomiak, M Diabetes-Care. 1990 October; 13(10): 1074-7 0149-5992

- **Slow gastric emptying in type I diabetes: relation to autonomic and peripheral neuropathy, blood glucose, and glycemic control.**
  Author(s): Department of Surgery, University of Vienna, Austria.
  Source: Merio, R Festa, A Bergmann, H Eder, T Eibl, N Stacher Janotta, G Weber, U Budka, C Heckenberg, A Bauer, P Francesconi, M Schernthaner, G Stacher, G Diabetes-Care. 1997 March; 20(3): 419-23 0149-5992

The following information is typical of that found when using the "Full IBIDS Database" to search for "peripheral neuropathy" (or a synonym):

- **A clinical study on treatment of diabetic peripheral neuropathy with tang zhi min capsules.**
  Author(s): Baoding Municipal Hospital of Traditional Chinese Medicine, Baoding 071000, Hebei Province.
  Source: Ren, H J-Tradit-Chin-Med. 2000 December; 20(4): 258-61 0254-6272

- **A combination of autoimmune hepatitis, sensory-dominant peripheral neuropathy, and primary Sjogren's syndrome in the same patient: a rare association.**
  Author(s): Department of Neurology, Institute of Clinical Medicine, University of Tuskuba, Tsukuba City, Japan.
  Source: Hoshino, S Yoshizawa, T Hayashi, A Ohkoshi, N Tamaoka, A Shoji, S J-Med. 1999; 30(1-2): 83-92 0025-7850

- **A novel antioxidant alleviates heat hyperalgesia in rats with an experimental painful peripheral neuropathy.**
  Author(s): Department of Anatomy, Hebrew University-Hadassah Dental and Medical School, Jerusalem, Israel.
  Source: Tal, M Neuroreport. 1996 May 31; 7(8): 1382-4 0959-4965

- **Absence of major peripheral neuropathy in a phase II trial of ifosfamide with vinorelbine in patients with ovarian cancer previously treated with platinum and paclitaxel.**
  Author(s): Department of Medicine, University of Chicago, Illinois, USA. gfleming@medicine.bsd.uchicago.edu

Source: Fleming, G F Waggoner, S E Rotmensch, J Langhauser, C Am-J-Clin-Oncol. 2001 February; 24(1): 52-7 0277-3732

- **An uncommon cause of peripheral neuropathy.**
  Author(s): Department of Internal Medicine, University of Missouri-Kansas City School of Medicine, 64139, USA.
  Source: Pandya, N Byler, M Armistead, S Arch-Fam-Med. 1998 Jan-February; 7(1): 85-7 1063-3987

- **Chemotherapy-induced peripheral neuropathy.**
  Author(s): Department of Neurology, Karl-Franzens Universitat Graz, Austria. Stefan.Quasthoff@kfunigraz.ac.at
  Source: Quasthoff, S Hartung, H P J-Neurol. 2002 January; 249(1): 9-17 0340-5354

- **Clinical observation on treatment of diabetic peripheral neuropathy with reinforced tianma duzhong capsule.**
  Author(s): Beijing Hospital.
  Source: Li, M Wang, X J-Tradit-Chin-Med. 1999 September; 19(3): 182-4 0254-6272

- **Coeliac disease associated with peripheral neuropathy in a child: a case report.**
  Author(s): Department of Neurological and Visual Sciences, University of Verona, Italy.
  Source: Simonati, A Battistella, P A Guariso, G Clementi, M Rizzuto, N Neuropediatrics. 1998 June; 29(3): 155-8 0174-304X

- **Dextromethorphan potentiates the effect of morphine in rats with peripheral neuropathy.**
  Author(s): Karolinska Institute, Department of Medical Laboratory Sciences and Technology, University Hospital, Huddinge, Sweden.
  Source: Kauppila, T Xu, X J Yu, W Wiesenfeld Hallin, Z Neuroreport. 1998 April 20; 9(6): 1071-4 0959-4965

- **Diagnosis, classification, and treatment of diabetic peripheral neuropathy.**
  Author(s): Deaconess-Joslin Foot Center, Boston, Massachusetts, USA.
  Source: Veves, A Sarnow, M R Clin-Podiatr-Med-Surg. 1995 January; 12(1): 19-30 0891-8422

- **Improvement of peripheral neuropathy by testosterone in a patient with 48,XXYY syndrome.**
  Author(s): Department of Rehabilitation Medicine, Tokai University School of Medicine, Kanagawa, Japan.
  Source: Izumi, S Tsubahara, A Tokai-J-Exp-Clin-Med. 2000 June; 25(2): 39-44 0385-0005

- **Management of peripheral neuropathy in diabetes mellitus. Recent research findings and their therapeutic implications.**
  Source: Martin, R A Postgrad-Med. 1987 September 1; 82(3): 183-7 0032-5481

- **Peripheral neuropathy following high-dose etoposide and autologous bone marrow transplantation.**
  Author(s): University of Toronto Autologous Bone Marrow Transplant Program, Toronto Hospital, Canada.
  Source: Imrie, K R Couture, F Turner, C C Sutcliffe, S B Keating, A Bone-Marrow-Transplant. 1994 January; 13(1): 77-9 0268-3369

- **Reduction of paclitaxel-induced peripheral neuropathy with glutamine.**
  Author(s): Division of Medical Oncology and Hematology, Department of Medicine, The Herbert Irving Comprehensive Cancer Center of Columbia University College of Physicians and Surgeons, New York, New York 10032, USA. vahdat@cuccfa.ccc.columbia.edu

Source: Vahdat, L Papadopoulos, K Lange, D Leuin, S Kaufman, E Donovan, D Frederick, D Bagiella, E Tiersten, A Nichols, G Garrett, T Savage, D Antman, K Hesdorffer, C S Balmaceda, C Clin-Cancer-Res. 2001 May; 7(5): 1192-7 1078-0432

- **Reversible peripheral neuropathy in idiopathic hypoparathyroidism.**
  Author(s): Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi, India.
  Source: Goswami, R Bhatia, M Goyal, R Kochupillai, N Acta-Neurol-Scand. 2002 February; 105(2): 128-31 0001-6314

- **Role of protein kinase Cepsilon and protein kinase A in a model of paclitaxel-induced painful peripheral neuropathy in the rat.**
  Author(s): Department of Medicine, Division of Neuroscience and Biomedical Sciences Program, NIH Pain Center (UCSF), University of California at San Francisco, San Francisco, CA 94143-0440, USA.
  Source: Dina, O A Chen, X Reichling, D Levine, J D Neuroscience. 2001; 108(3): 507-15 0306-4522

- **Role of thiamine deficiency in the pathogenesis of alcoholic peripheral neuropathy and the Wernicke-Korsakoff Syndrome: an update.**
  Source: Butterworth, R.F. D'Amour, M. Bruneau, J. Heroux, M. Brissette, S. NATO-ASI-Ser-Ser-A-Life-Sci. New York, N.Y. : Plenum Press. 1991. volume 206 page 269-273.

- **Sensory peripheral neuropathy of vitamin B12 deficiency: a primary demyelinating disease?**
  Author(s): Department of Neurology, Hadassah University Hospital, Jerusalem, Israel.
  Source: Steiner, I Kidron, D Soffer, D Wirguin, I Abramsky, O J-Neurol. 1988 January; 235(3): 163-4 0340-5354

- **Spontaneous age-related peripheral neuropathy in B6C3F1 mice.**
  Author(s): Safety Research Laboratories, Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan.
  Source: Tabata, H Ikegami, H Kariya, K J-Toxicol-Sci. 2000 May; 25(2): 95-104 0388-1350

- **Successful treatment of peripheral neuropathy with chemotherapy in osteosclerotic myeloma.**
  Source: Parra, R Fernandez, J M Garcia Bragado, F Bueno, J Biosca, M J-Neurol. 1987 May; 234(4): 261-3 0340-5354

- **Treatment of symptomatic diabetic peripheral neuropathy with the anti-oxidant alpha-lipoic acid. A 3-week multicentre randomized controlled trial (ALADIN Study).**
  Author(s): Diabetes-Forschungsinstitut an der Heinrich-Heine-Universitat, Dusseldorf, Germany.
  Source: Ziegler, D Hanefeld, M Ruhnau, K J Meissner, H P Lobisch, M Schutte, K Gries, F A Diabetologia. 1995 December; 38(12): 1425-33 0012-186X

- **Trigeminal and peripheral neuropathy in a patient with systemic sclerosis and silicosis.**
  Author(s): Department of Medicine, All India Institute of Medical Sciences, New Delhi.
  Source: Agarwal, R Vasan, R S Singh, R R Saxena, S P Bhadoria, D P Srivastava, A K Verma, A Tiwari, S C Malaviya, A N Clin-Exp-Rheumatol. 1987 Oct-December; 5(4): 375-6 0392-856X

## Federal Resources on Nutrition

In addition to the IBIDS, the United States Department of Health and Human Services (HHS) and the United States Department of Agriculture (USDA) provide many sources of information on general nutrition and health. Recommended resources include:

- healthfinder®, HHS's gateway to health information, including diet and nutrition: **http://www.healthfinder.gov/scripts/SearchContext.asp?topic=238&page=0**
- The United States Department of Agriculture's Web site dedicated to nutrition information: **www.nutrition.gov**
- The Food and Drug Administration's Web site for federal food safety information: **www.foodsafety.gov**
- The National Action Plan on Overweight and Obesity sponsored by the United States Surgeon General: **http://www.surgeongeneral.gov/topics/obesity/**
- The Center for Food Safety and Applied Nutrition has an Internet site sponsored by the Food and Drug Administration and the Department of Health and Human Services: **http://vm.cfsan.fda.gov/**
- Center for Nutrition Policy and Promotion sponsored by the United States Department of Agriculture: **http://www.usda.gov/cnpp/**
- Food and Nutrition Information Center, National Agricultural Library sponsored by the United States Department of Agriculture: **http://www.nal.usda.gov/fnic/**
- Food and Nutrition Service sponsored by the United States Department of Agriculture: **http://www.fns.usda.gov/fns/**

## Additional Web Resources

A number of additional Web sites offer encyclopedic information covering food and nutrition. The following is a representative sample:

- AOL: **http://search.aol.com/cat.adp?id=174&layer=&from=subcats**
- Family Village: **http://www.familyvillage.wisc.edu/med_nutrition.html**
- Google: **http://directory.google.com/Top/Health/Nutrition/**
- Healthnotes: **http://www.healthnotes.com/**
- Open Directory Project: **http://dmoz.org/Health/Nutrition/**
- Yahoo.com: **http://dir.yahoo.com/Health/Nutrition/**
- WebMD®Health: **http://my.webmd.com/nutrition**
- WholeHealthMD.com: **http://www.wholehealthmd.com/reflib/0,1529,00.html**

The following is a specific Web list relating to peripheral neuropathy; please note that any particular subject below may indicate either a therapeutic use, or a contraindication (potential danger), and does not reflect an official recommendation:

- **Vitamins**

  **Pyridoxine**
  Source: Integrative Medicine Communications; www.drkoop.com

  **Vitamin B6**
  Source: Prima Communications, Inc.www.personalhealthzone.com

  **Vitamin B6 (pyridoxine)**
  Source: Integrative Medicine Communications; www.drkoop.com

- **Minerals**

  **Acetyl-l-carnitine**
  Source: Healthnotes, Inc.; www.healthnotes.com

  **Biotin**
  Source: Healthnotes, Inc.; www.healthnotes.com

  **Biotin**
  Source: Integrative Medicine Communications; www.drkoop.com

  **Biotin**
  Source: Prima Communications, Inc.www.personalhealthzone.com

  **Vitamin H (biotin)**
  Source: Integrative Medicine Communications; www.drkoop.com

- **Food and Diet**

  **Diabetes**
  Source: Healthnotes, Inc.; www.healthnotes.com

# CHAPTER 3. ALTERNATIVE MEDICINE AND PERIPHERAL NEUROPATHY

## Overview

In this chapter, we will begin by introducing you to official information sources on complementary and alternative medicine (CAM) relating to peripheral neuropathy. At the conclusion of this chapter, we will provide additional sources.

## National Center for Complementary and Alternative Medicine

The National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (**http://nccam.nih.gov/**) has created a link to the National Library of Medicine's databases to facilitate research for articles that specifically relate to peripheral neuropathy and complementary medicine. To search the database, go to the following Web site: **http://www.nlm.nih.gov/nccam/camonpubmed.html**. Select "CAM on PubMed." Enter "peripheral neuropathy" (or synonyms) into the search box. Click "Go." The following references provide information on particular aspects of complementary and alternative medicine that are related to peripheral neuropathy:

- **A clinical study on treatment of diabetic peripheral neuropathy with tang zhi min capsules.**
  Author(s): Ren H.
  Source: J Tradit Chin Med. 2000 December; 20(4): 258-61. No Abstract Available.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11263276&dopt=Abstract

- **A painful peripheral neuropathy in the rat produced by the chemotherapeutic drug, paclitaxel.**
  Author(s): Polomano RC, Mannes AJ, Clark US, Bennett GJ.
  Source: Pain. 2001 December; 94(3): 293-304.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11731066&dopt=Abstract

- **Absence of major peripheral neuropathy in a phase II trial of ifosfamide with vinorelbine in patients with ovarian cancer previously treated with platinum and paclitaxel.**
  Author(s): Fleming GF, Waggoner SE, Rotmensch J, Langhauser C.
  Source: American Journal of Clinical Oncology : the Official Publication of the American Radium Society. 2001 February; 24(1): 52-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11232950&dopt=Abstract

- **Altered temporal pattern of evoked afferent activity in a rat model of vincristine-induced painful peripheral neuropathy.**
  Author(s): Tanner KD, Reichling DB, Gear RW, Paul SM, Levine JD.
  Source: Neuroscience. 2003; 118(3): 809-17.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12710988&dopt=Abstract

- **BGP-15, a hydroximic acid derivative, protects against cisplatin- or taxol-induced peripheral neuropathy in rats.**
  Author(s): Bardos G, Moricz K, Jaszlits L, Rabloczky G, Tory K, Racz I, Bernath S, Sumegi B, Farkas B, Literati-Nagy B, Literati-Nagy P.
  Source: Toxicology and Applied Pharmacology. 2003 July 1; 190(1): 9-16.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12831778&dopt=Abstract

- **Botanicals and dietary supplements in diabetic peripheral neuropathy.**
  Author(s): Halat KM, Dennehy CE.
  Source: The Journal of the American Board of Family Practice / American Board of Family Practice. 2003 January-February; 16(1): 47-57. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12583650&dopt=Abstract

- **Chemotherapy-induced peripheral neuropathy.**
  Author(s): Quasthoff S, Hartung HP.
  Source: Journal of Neurology. 2002 January; 249(1): 9-17. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11954874&dopt=Abstract

- **Clinical observation on treatment of diabetic peripheral neuropathy with reinforced tianma duzhong capsule.**
  Author(s): Li M, Wang X.
  Source: J Tradit Chin Med. 1999 September; 19(3): 182-4. No Abstract Available.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10921146&dopt=Abstract

- **Damage to the cytoskeleton of large diameter sensory neurons and myelinated axons in vincristine-induced painful peripheral neuropathy in the rat.**
  Author(s): Topp KS, Tanner KD, Levine JD.

Source: The Journal of Comparative Neurology. 2000 September 4; 424(4): 563-76.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10931481&dopt=Abstract

- **Different peripheral mechanisms mediate enhanced nociception in metabolic/toxic and traumatic painful peripheral neuropathies in the rat.**
  Author(s): Aley KO, Levine JD.
  Source: Neuroscience. 2002; 111(2): 389-97.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11983324&dopt=Abstract

- **Fulminant peripheral neuropathy with severe quadriparesis associated with vincristine therapy.**
  Author(s): Moudgil SS, Riggs JE.
  Source: The Annals of Pharmacotherapy. 2000 October; 34(10): 1136-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11054980&dopt=Abstract

- **Long-lasting effect of transcutaneous electrical nerve stimulation on the thermal hyperalgesia in the rat model of peripheral neuropathy.**
  Author(s): Inoue T, Takenoshita M, Shibata M, Nishimura M, Sakaue G, Shibata SC, Mashimo T.
  Source: Journal of the Neurological Sciences. 2003 July 15; 211(1-2): 43-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12767496&dopt=Abstract

- **Peripheral neuropathy due to biweekly paclitaxel, epirubicin and cisplatin in patients with advanced ovarian cancer.**
  Author(s): Postma TJ, Hoekman K, van Riel JM, Heimans JJ, Vermorken JB.
  Source: Journal of Neuro-Oncology. 1999; 45(3): 241-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10845395&dopt=Abstract

- **Peripheral neuropathy due to therapy with paclitaxel, gemcitabine, and cisplatin in patients with advanced ovarian cancer.**
  Author(s): Verstappen CC, Postma TJ, Hoekman K, Heimans JJ.
  Source: Journal of Neuro-Oncology. 2003 June; 63(2): 201-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12825825&dopt=Abstract

- **Peripheral neuropathy.**
  Author(s): Bowers M.
  Source: Beta. 1997 March; : 14-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11364522&dopt=Abstract

- **Peripheral neuropathy: alternative and complementary options.**
  Author(s): Huebscher R.

Source: Nurse Pract Forum. 2000 June; 11(2): 73-7. Review. No Abstract Available.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11220057&dopt=Abstract

- **Phase II clinical trial of carboplatin and docetaxel in patients with metastatic ovarian cancer: active combination with low incidence of peripheral neuropathy.**
  Author(s): Vorobiof DA, Rapoport BL, Chasen MR, Cohen GL, Mahomed R, Karime M.
  Source: International Journal of Gynecological Cancer : Official Journal of the International Gynecological Cancer Society. 2003 May-June; 13(3): 287-91.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12801257&dopt=Abstract

- **Reduction of paclitaxel-induced peripheral neuropathy with glutamine.**
  Author(s): Vahdat L, Papadopoulos K, Lange D, Leuin S, Kaufman E, Donovan D, Frederick D, Bagiella E, Tiersten A, Nichols G, Garrett T, Savage D, Antman K, Hesdorffer CS, Balmaceda C.
  Source: Clinical Cancer Research : an Official Journal of the American Association for Cancer Research. 2001 May; 7(5): 1192-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11350883&dopt=Abstract

- **Role of protein kinase Cepsilon and protein kinase A in a model of paclitaxel-induced painful peripheral neuropathy in the rat.**
  Author(s): Dina OA, Chen X, Reichling D, Levine JD.
  Source: Neuroscience. 2001; 108(3): 507-15.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11738263&dopt=Abstract

- **Severe lead-induced peripheral neuropathy in a dialysis patient.**
  Author(s): Barats MS, Gonick HC, Rothenberg S, Balabanian M, Manton WI.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation. 2000 May; 35(5): 963-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10793035&dopt=Abstract

- **Sexual dimorphism for protein kinase c epsilon signaling in a rat model of vincristine-induced painful peripheral neuropathy.**
  Author(s): Joseph EK, Levine JD.
  Source: Neuroscience. 2003; 119(3): 831-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12809704&dopt=Abstract

- **The WldS protein protects against axonal degeneration: a model of gene therapy for peripheral neuropathy.**
  Author(s): Wang MS, Fang G, Culver DG, Davis AA, Rich MM, Glass JD.
  Source: Annals of Neurology. 2001 December; 50(6): 773-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11761475&dopt=Abstract

- **Vitamin B6 supplementation can improve peripheral polyneuropathy in patients with chronic renal failure on high-flux haemodialysis and human recombinant erythropoietin.**
  Author(s): Okada H, Moriwaki K, Kanno Y, Sugahara S, Nakamoto H, Yoshizawa M, Suzuki H.
  Source: Nephrology, Dialysis, Transplantation : Official Publication of the European Dialysis and Transplant Association - European Renal Association. 2000 September; 15(9): 1410-3.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10978399&dopt=Abstract

## Additional Web Resources

A number of additional Web sites offer encyclopedic information covering CAM and related topics. The following is a representative sample:

- Alternative Medicine Foundation, Inc.: **http://www.herbmed.org/**
- AOL: **http://search.aol.com/cat.adp?id=169&layer=&from=subcats**
- Chinese Medicine: **http://www.newcenturynutrition.com/**
- drkoop.com®: **http://www.drkoop.com/InteractiveMedicine/IndexC.html**
- Family Village: **http://www.familyvillage.wisc.edu/med_altn.htm**
- Google: **http://directory.google.com/Top/Health/Alternative/**
- Healthnotes: **http://www.healthnotes.com/**
- MedWebPlus: **http://medwebplus.com/subject/Alternative_and_Complementary_Medicine**
- Open Directory Project: **http://dmoz.org/Health/Alternative/**
- HealthGate: **http://www.tnp.com/**
- WebMD®Health: **http://my.webmd.com/drugs_and_herbs**
- WholeHealthMD.com: **http://www.wholehealthmd.com/reflib/0,1529,00.html**
- Yahoo.com: **http://dir.yahoo.com/Health/Alternative_Medicine/**

The following is a specific Web list relating to peripheral neuropathy; please note that any particular subject below may indicate either a therapeutic use, or a contraindication (potential danger), and does not reflect an official recommendation:

- **General Overview**

  **AIDS and HIV**
  Source: Integrative Medicine Communications; www.drkoop.com

  **Bell's Palsy**
  Source: Healthnotes, Inc.; www.healthnotes.com

**Celiac Disease**
Source: Healthnotes, Inc.; www.healthnotes.com

**Diabetes**
Source: Prima Communications, Inc.www.personalhealthzone.com

**AIDS and HIV Support**
Source: Healthnotes, Inc.; www.healthnotes.com

**Multiple Sclerosis**
Source: Healthnotes, Inc.; www.healthnotes.com

**Serum Sickness**
Source: Integrative Medicine Communications; www.drkoop.com

- **Herbs and Supplements**

**Betaine**
Alternative names: Trimethylglycine
Source: Integrative Medicine Communications; www.drkoop.com

**Didanosine**
Source: Healthnotes, Inc.; www.healthnotes.com

**Evening Primrose**
Alternative names: Oenothera biennis, Sun Drop
Source: Integrative Medicine Communications; www.drkoop.com

**Gamma-Linolenic Acid (GLA)**
Source: Integrative Medicine Communications; www.drkoop.com

**GLA**
Source: Integrative Medicine Communications; www.drkoop.com

**GLA (Gamma-Linolenic Acid)**
Source: Prima Communications, Inc.www.personalhealthzone.com

**Isoniazid**
Source: Healthnotes, Inc.; www.healthnotes.com

**Lipoic Acid**
Source: Prima Communications, Inc.www.personalhealthzone.com

**MAO Inhibitors**
Source: Prima Communications, Inc.www.personalhealthzone.com

**Methionine**
Source: Healthnotes, Inc.; www.healthnotes.com

**Oenothera Biennis**
Source: Integrative Medicine Communications; www.drkoop.com

**Phenelzine**
Source: Healthnotes, Inc.; www.healthnotes.com

**Sun Drop**
Source: Integrative Medicine Communications; www.drkoop.com

**Trimethylglycine**
Source: Integrative Medicine Communications; www.drkoop.com

## General References

A good place to find general background information on CAM is the National Library of Medicine. It has prepared within the MEDLINEplus system an information topic page dedicated to complementary and alternative medicine. To access this page, go to the MEDLINEplus site at **http://www.nlm.nih.gov/medlineplus/alternativemedicine.html**. This Web site provides a general overview of various topics and can lead to a number of general sources.

# CHAPTER 4. DISSERTATIONS ON PERIPHERAL NEUROPATHY

## Overview

In this chapter, we will give you a bibliography on recent dissertations relating to peripheral neuropathy. We will also provide you with information on how to use the Internet to stay current on dissertations. **IMPORTANT NOTE:** When following the search strategy described below, you may discover non-medical dissertations that use the generic term "peripheral neuropathy" (or a synonym) in their titles. To accurately reflect the results that you might find while conducting research on peripheral neuropathy, we have not necessarily excluded non-medical dissertations in this bibliography.

## Dissertations on Peripheral Neuropathy

*ProQuest Digital Dissertations*, the largest archive of academic dissertations available, is located at the following Web address: **http://wwwlib.umi.com/dissertations**. From this archive, we have compiled the following list covering dissertations devoted to peripheral neuropathy. You will see that the information provided includes the dissertation's title, its author, and the institution with which the author is associated. The following covers recent dissertations found when using this search procedure:

- **Characterization of Chemotherapy-Induced Peripheral Neuropathy** by Visovsky, Constance Grace; Phd from Case Western Reserve University (health Sciences), 2002, 123 pages
  http://wwwlib.umi.com/dissertations/fullcit/3061318

## Keeping Current

Ask the medical librarian at your library if it has full and unlimited access to the *ProQuest Digital Dissertations* database. From the library, you should be able to do more complete searches via **http://wwwlib.umi.com/dissertations**.

# CHAPTER 5. CLINICAL TRIALS AND PERIPHERAL NEUROPATHY

## Overview

In this chapter, we will show you how to keep informed of the latest clinical trials concerning peripheral neuropathy.

## Recent Trials on Peripheral Neuropathy

The following is a list of recent trials dedicated to peripheral neuropathy.[8] Further information on a trial is available at the Web site indicated.

- **Amifostine in Treating Peripheral Neuropathy in Patients Who Have Undergone Chemotherapy for Cancer**

  Condition(s): Neurotoxicity

  Study Status: This study is currently recruiting patients.

  Sponsor(s): Gynecologic Oncology Group; National Cancer Institute (NCI)

  Purpose - Excerpt: RATIONALE: Amifostine may be effective in relieving numbness, tingling, and other symptoms of peripheral neuropathy. It is not yet known whether amifostine is effective in treating peripheral neuropathy in patients who have received chemotherapy for cancer. PURPOSE: Randomized phase III trial to study the effectiveness of amifostine in relieving numbness, tingling, and other symptoms of peripheral neuropathy in patients who have undergone platinum-based chemotherapy (such as cisplatin or carboplatin) for cancer.

  Phase(s): Phase III

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00058071

[8] These are listed at **www.ClinicalTrials.gov**.

- **Gabapentin in Treating Peripheral Neuropathy in Cancer Patients Undergoing Chemotherapy**

  Condition(s): Neurotoxicity; Pain; Quality of Life

  Study Status: This study is currently recruiting patients.

  Sponsor(s): North Central Cancer Treatment Group; National Cancer Institute (NCI)

  Purpose - Excerpt: RATIONALE: Gabapentin may be effective in relieving pain and other symptoms of peripheral neuropathy. It is not yet known if gabapentin is effective in treating peripheral neuropathy in cancer patients undergoing chemotherapy. PURPOSE: Randomized phase III trial to determine the effectiveness of gabapentin in treating pain and other symptoms of peripheral neuropathy in cancer patients undergoing chemotherapy.

  Phase(s): Phase III

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00027963

- **LY333531 Treatment for Symptomatic Peripheral Neuropathy in Patients with Diabetes.**

  Condition(s): Diabetic Neuropathies; Diabetes Mellitus, Insulin-Dependent; Diabetes Mellitus, Non-Insulin-Dependent

  Study Status: This study is currently recruiting patients.

  Sponsor(s): Eli Lilly and Company

  Purpose - Excerpt: The purpose of this protocol is to determine if an investigational drug known as LY333531 is effective in treating nerve malfunction in diabetes.

  Phase(s): Phase III

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00044408

- **Neotrofin for treatment of chemotherapy-induced peripheral neuropathy**

  Condition(s): Peripheral Nervous System Diseases; Chemotherapy-Induced Peripheral Neuropathy

  Study Status: This study is currently recruiting patients.

  Sponsor(s): NeoTherapeutics

  Purpose - Excerpt: This study will assess the safety and efficacy of Neotrofin in treating the peripheral neuropathy that results from chemotherapy for cancer.

  Phase(s): Phase II

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00041795

- **Treatment for Symptomatic Peripheral Neuropathy in Patients with Diabetes.**

  Condition(s): Diabetic Neuropathies; Diabetes Mellitus

  Study Status: This study is currently recruiting patients.

  Sponsor(s): Eli Lilly and Company

  Purpose - Excerpt: The purpose of this protocol is to determine if an investigational drug is effective in treating nerve malfunction in diabetes.

  Phase(s): Phase III

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00044395

- **Treatment of Peripheral Neuropathy in Patients with Diabetes.**

  Condition(s): Diabetic Neuropathies; Diabetes Mellitus

  Study Status: This study is currently recruiting patients.

  Sponsor(s): Eli Lilly and Company

  Purpose - Excerpt: The purpose of this protocol is to determine if an investigational drug is effective in treating nerve malfunction in diabetes.

  Phase(s): Phase III

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00044421

- **A study of Rituxan in the treatment of polyneuropathies associated with serum IgM autoantibodies**

  Condition(s): Peripheral Neuropathy

  Study Status: This study is no longer recruiting patients.

  Sponsor(s): National Center for Research Resources (NCRR); Genentech

  Purpose - Excerpt: Peripheral neuropathies cause weakness and sensory loss that can produce severe disability. Some neuropathies are immune-mediated and associated with antibodies. It has been postulated that Rituxan treatment may reduce the level of antibody production limiting the loss of muscle strength and hence improve activities of daily living. The purpose of this open-label study (all participants get Rituxan and not placebo) is to determine the safety and effectiveness of Rituxan in the treatment of polyneuropathies associated with serum IgM autoantibodies in those who have already been treated with one course of Rituxan. Subjects will be treated on the in-patient Clinical Research Center with Rituxan for two treatments one week a part and then individual treatments every 10 weeks for one year. The effectiveness of Rituxan will be followed by looking for increases in muscle strength and decreases in the serum IgM autoantibodies.

  Phase(s): Phase II

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00006072

- **The Efficacy of a Standardized Acupuncture Regimen and Amitriptyline Compared With Placebo as a Treatment for Pain Caused by Peripheral Neuropathy in HIV-Infected Patients**

  Condition(s): HIV Infections; Peripheral Nervous System Disease

  Study Status: This study is no longer recruiting patients.

  Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID)

  Purpose - Excerpt: To evaluate the separate and combined efficacy of a standardized acupuncture regimen and amitriptyline on the relief of pain due to peripheral neuropathy and on the quality of life of HIV-infected patients. Both amitriptyline, an antidepressant, and acupuncture, a Chinese medical approach that uses needles to relieve pain, have been used successfully to reduce pain in some people. It is not known how effectively these approaches relieve or reduce pain in patients with peripheral neuropathy secondary to HIV infection.

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00000817

- **Acetyl-L-Carnitine for the Treatment of NRTI-Associated Peripheral Neuropathy**

  Condition(s): HIV Infections; Peripheral Nervous System Diseases

  Study Status: This study is not yet open for patient recruitment.

  Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID); Neurologic AIDS Research Consortium (NARC)

  Purpose - Excerpt: The purpose of this study is to determine if acetyl-L-carnitine (ALC) reduces pain, numbness, and tingling in the feet and legs of patients with nucleoside reverse transcriptase inhibitor (NRTI)-associated peripheral neuropathy. Another purpose is to determine if ALC is safe and tolerable in HIV patients who have taken certain anti-HIV drugs.

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00050271

- **Achilles Tendon Lengthening in Patients with Diabetes to Prevent Foot Ulcers**

  Condition(s): Diabetes Mellitus; Foot Ulcer; Peripheral Neuropathy

  Study Status: This study is completed.

  Sponsor(s): National Institute of Child Health and Human Development (NICHD)

  Purpose - Excerpt: People with diabetes often develop severe skin problems (ulcers) on their feet. Sometimes these are treated with surgery and other times by temporarily immobilizing the foot in a cast. This study compares the effect of surgery to lengthen the Achilles tendon and put the foot in a cast, to using a cast alone. The study will also examine how foot strength, joint movement, and overall ability to walk, balance and climb stairs is affected.

  Phase(s): Phase I

  Study Type: Interventional

  Contact(s): see Web site below

Web Site: http://clinicaltrials.gov/ct/show/NCT00006426

- **HIV-Related Peripheral Neuropathy**

  Condition(s): Peripheral Nervous System Diseases; HIV Infections

  Study Status: This study is not yet open for patient recruitment.

  Sponsor(s): Center for Medicinal Cannabis Research; University of California, San Francisco; Community Consortium

  Purpose - Excerpt: To evaluate whether smoked marijuana reduces pain in people with HIV-related peripheral neuropathy.

  Phase(s): Phase II

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00046722

- **Intranasal Peptide T in the Treatment of Painful Peripheral Neuropathy of AIDS**

  Condition(s): HIV Infections; Peripheral Nervous System Disease

  Study Status: This study is completed.

  Sponsor(s): Advanced Peptides

  Purpose - Excerpt: To compare the effects of intranasal peptide T and placebo in the treatment of painful peripheral neuropathy associated with human immunodeficiency virus (HIV) infection.

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00002083

- **Lamotrigine in Treating Peripheral Neuropathy Caused by Chemotherapy in Patients With Cancer**

  Condition(s): Quality of Life; neurotoxicity; Pain; unspecified adult solid tumor, protocol specific

  Study Status: This study is not yet open for patient recruitment.

  Sponsor(s): North Central Cancer Treatment Group; National Cancer Institute (NCI)

  Purpose - Excerpt: RATIONALE: Lamotrigine may be effective in reducing pain, numbness, tingling, and other symptoms of peripheral neuropathy. It is not yet known whether lamotrigine is effective in treating peripheral neuropathy caused by chemotherapy. PURPOSE: Randomized phase III trial to study the effectiveness of lamotrigine in reducing pain, numbness, tingling, and other symptoms of peripheral neuropathy caused by chemotherapy in patients who have cancer.

  Phase(s): Phase III

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00068445

## Keeping Current on Clinical Trials

The U.S. National Institutes of Health, through the National Library of Medicine, has developed ClinicalTrials.gov to provide current information about clinical research across the broadest number of diseases and conditions.

The site was launched in February 2000 and currently contains approximately 5,700 clinical studies in over 59,000 locations worldwide, with most studies being conducted in the United States. ClinicalTrials.gov receives about 2 million hits per month and hosts approximately 5,400 visitors daily. To access this database, simply go to the Web site at **http://www.clinicaltrials.gov/** and search by "peripheral neuropathy" (or synonyms).

While ClinicalTrials.gov is the most comprehensive listing of NIH-supported clinical trials available, not all trials are in the database. The database is updated regularly, so clinical trials are continually being added. The following is a list of specialty databases affiliated with the National Institutes of Health that offer additional information on trials:

- For clinical studies at the Warren Grant Magnuson Clinical Center located in Bethesda, Maryland, visit their Web site: **http://clinicalstudies.info.nih.gov/**
- For clinical studies conducted at the Bayview Campus in Baltimore, Maryland, visit their Web site: **http://www.jhbmc.jhu.edu/studies/index.html**
- For cancer trials, visit the National Cancer Institute: **http://cancertrials.nci.nih.gov/**
- For eye-related trials, visit and search the Web page of the National Eye Institute: **http://www.nei.nih.gov/neitrials/index.htm**
- For heart, lung and blood trials, visit the Web page of the National Heart, Lung and Blood Institute: **http://www.nhlbi.nih.gov/studies/index.htm**
- For trials on aging, visit and search the Web site of the National Institute on Aging: **http://www.grc.nia.nih.gov/studies/index.htm**
- For rare diseases, visit and search the Web site sponsored by the Office of Rare Diseases: **http://ord.aspensys.com/asp/resources/rsch_trials.asp**
- For alcoholism, visit the National Institute on Alcohol Abuse and Alcoholism: **http://www.niaaa.nih.gov/intramural/Web_dicbr_hp/particip.htm**
- For trials on infectious, immune, and allergic diseases, visit the site of the National Institute of Allergy and Infectious Diseases: **http://www.niaid.nih.gov/clintrials/**
- For trials on arthritis, musculoskeletal and skin diseases, visit newly revised site of the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health: **http://www.niams.nih.gov/hi/studies/index.htm**
- For hearing-related trials, visit the National Institute on Deafness and Other Communication Disorders: **http://www.nidcd.nih.gov/health/clinical/index.htm**
- For trials on diseases of the digestive system and kidneys, and diabetes, visit the National Institute of Diabetes and Digestive and Kidney Diseases: **http://www.niddk.nih.gov/patient/patient.htm**
- For drug abuse trials, visit and search the Web site sponsored by the National Institute on Drug Abuse: **http://www.nida.nih.gov/CTN/Index.htm**

- For trials on mental disorders, visit and search the Web site of the National Institute of Mental Health: **http://www.nimh.nih.gov/studies/index.cfm**
- For trials on neurological disorders and stroke, visit and search the Web site sponsored by the National Institute of Neurological Disorders and Stroke of the NIH: **http://www.ninds.nih.gov/funding/funding_opportunities.htm#Clinical_Trials**

# CHAPTER 6. PATENTS ON PERIPHERAL NEUROPATHY

## Overview

Patents can be physical innovations (e.g. chemicals, pharmaceuticals, medical equipment) or processes (e.g. treatments or diagnostic procedures). The United States Patent and Trademark Office defines a patent as a grant of a property right to the inventor, issued by the Patent and Trademark Office.[9] Patents, therefore, are intellectual property. For the United States, the term of a new patent is 20 years from the date when the patent application was filed. If the inventor wishes to receive economic benefits, it is likely that the invention will become commercially available within 20 years of the initial filing. It is important to understand, therefore, that an inventor's patent does not indicate that a product or service is or will be commercially available. The patent implies only that the inventor has "the right to exclude others from making, using, offering for sale, or selling" the invention in the United States. While this relates to U.S. patents, similar rules govern foreign patents.

In this chapter, we show you how to locate information on patents and their inventors. If you find a patent that is particularly interesting to you, contact the inventor or the assignee for further information. **IMPORTANT NOTE:** When following the search strategy described below, you may discover non-medical patents that use the generic term "peripheral neuropathy" (or a synonym) in their titles. To accurately reflect the results that you might find while conducting research on peripheral neuropathy, we have not necessarily excluded non-medical patents in this bibliography.

## Patents on Peripheral Neuropathy

By performing a patent search focusing on peripheral neuropathy, you can obtain information such as the title of the invention, the names of the inventor(s), the assignee(s) or the company that owns or controls the patent, a short abstract that summarizes the patent, and a few excerpts from the description of the patent. The abstract of a patent tends to be more technical in nature, while the description is often written for the public. Full patent descriptions contain much more information than is presented here (e.g. claims, references, figures, diagrams, etc.). We will tell you how to obtain this information later in the chapter.

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[9] Adapted from the United States Patent and Trademark Office: **http://www.uspto.gov/web/offices/pac/doc/general/whatis.htm**.

The following is an example of the type of information that you can expect to obtain from a patent search on peripheral neuropathy:

- **Alkaline and acid phosphatase inhibitors in treatment of neurological disorders**

  Inventor(s): Eveleth; David D. (Mission Viejo, CA), Kelleher; Judith A. (Irvine, CA)

  Assignee(s): Cortex Pharmaceuticals, Inc. (Irvine, CA)

  Patent Number: 5,567,724

  Date filed: June 1, 1994

  Abstract: The present invention provides a method of inhibiting.beta.-amyloid toxicity in brain cells. The method includes administering to the cells an amount of an alkaline phosphatase inhibitor which is pharmacologically effective to reduce degeneration in the cells. Methods of treatment of **peripheral neuropathy** are also provided using acid or alkaline phosphatase inhibitors.

  Excerpt(s): The present invention relates to the use of alkaline and acid phosphatase inhibitors in the treatment of neurological disorders. More particularly, the present invention relates to the use of various specific phosphatase inhibitors in the treatment of.beta.-amyloid toxicity in brain cells and the use of phosphatase inhibitors in the treatment of **peripheral neuropathy.** Alzheimer's Disease (AD) is a progressive neurodegenerative condition affecting a substantial proportion of people over the age of 65. There is presently no known cure. One hallmark of AD neuropathology includes neurofibrillary tangles involving neuronal processes and closely associated with gliotic astrocytes and with macrophages. Another hallmark of AD is the presence in the brain of affected individuals of "plaques" composed of a variety of proteins, glycoproteins, and other components. These plaques always contain a high proportion of.beta.-amyloid peptide, a 42-43 amino acid peptide aberrantly cleaved from the amyloid precursor protein. Though normally observed in blood and cerebrospinal fluid,.beta.-amyloid peptide in an aggregated form is considered partly responsible for the noted neuronal death observed in AD (Koh, et al., Brain Res. 533:315 (1990); Mattson, et al., J. Neurosoi, 12:376 1992, etc.). Exposure of brain cells cultured in vitro to.beta.-amyloid peptide results in the degeneration of these cells. How this aggregated peptide mediates neuronal death is unclear, yet published reports suggest a programmed cell death or apoptotic mechanism. Loo, et al., PNAS, 90:7951 (1993).

  Web site: http://www.delphion.com/details?pn=US05567724__

- **Autoantibodies and their targets in the diagnosis of peripheral neuropathies**

  Inventor(s): Pestronk; Alan (St. Louis, MO)

  Assignee(s): Washington University (St. Louis, MO)

  Patent Number: 5,443,952

  Date filed: August 5, 1993

  Abstract: The present invention relates to methods of aiding in the diagnosis of **peripheral neuropathies** that comprise determining the titer of autoantibodies directed toward particular nervous system antigens. It also provides for substantially purified preparations of specific antigens, namely neuroprotein-1, neuroprotein-2, neuroprotein-3, neuroprotein-4 and neuroprotein-5, which may be used in such diagnostic methods.

Excerpt(s): The present invention relates to methods of diagnosing **peripheral neuropathies** that comprise determining the titer of antibodies directed toward particular nervous system antigens. It also provides for substantially purified preparations of specific antigens namely neuroprotein-1, neuroprotein-2, neuroprotein-3, neuroprotein-4 and neuroprotein-5, which may be used in such diagnostic methods. A patient who exhibits a disorder of one or more peripheral nerves is said to suffer from a **peripheral neuropathy.** Peripheral nerves extend beyond the brain and spinal cord into tissues that lie outside the central nervous system to provide a bidirectional communication network. They serve as conduits of impulses from the brain and spinal cord to the rest of the body; for example, motor neurons carry signals to direct movement. Peripheral nerves are also capable of transmitting sensory information gathered by specialized receptors to the brain. In short, peripheral nerves provide the connection between brain, body, and environment, and serve to coordinate the relationship between an organism's brain and the outside world. A **peripheral neuropathy** may manifest itself in a number of ways. If a motor nerve is affected, the patient may exhibit weakness in the muscle groups supplied by that nerve. If a sensory nerve is involved, the patient may experience numbness, tingling, loss of sensitivity to temperature, touch, and/or vibration, or even increased sensitivity in the area innervated by the diseased nerve.

Web site: http://www.delphion.com/details?pn=US05443952__

- **Diagnostic apparatus and method for evaluation of carpal tunnel syndrome**

  Inventor(s): Williams; George Roger (3024 SE. 40th St., Edmond, OK 73013)

  Assignee(s): none reported

  Patent Number: 6,045,517

  Date filed: April 7, 1998

  Abstract: This invention is a diagnostic device for measuring the extensibility of certain key carpal ligaments so as to determine the tendency of the subject to carpal tunnel damage. It consists of a structure to secure the arm and hand in a predetermined position on a stationary platform and the metacarpals of the hand in a predetermined position on a carriage moveable relative to the platform, so that the radius and ulnar bones of the forearm may be aligned in a fixed plane parallel with the moveable plane of the metacarpals of the hand. Once secure, a force is applied to the carriage in a dorsal direction perpendicular to the metacarpal plane, so as to measure the metacarpal glide. This force places stress on the ligaments of the volar joint between the proximal and distal carpal row, and resulting displacement, tension, and creep strength values are measured by a load cell and a lineometer. Using these values, the following can be determined: (1) extent of volar carpal ligament contracture and deformity; (2) requirements of ligament retraining; (3) diagnostic criteria for predicting carpal tunnel syndrome; and (4) values to assist health professionals in determining whether or not surgery for decompressing **peripheral neuropathy** is warranted.

  Excerpt(s): This invention relates generally to medical diagnostic devices. More particularly, the present invention provides an apparatus and a method for measuring the tension of carpal ligaments under applied translation forces which in turn will provide indicators of future or existing carpal tunnel syndrome. Carpal tunnel syndrome is a condition in which the median nerve is compressed by the surrounding contents of the median nerve canal. This condition is believed to be caused by a biomechanical ligament imbalance in the volar carpal ligaments, which is in turn related

to the increased ratio of power produced by the flexor muscles over extensor muscles as they interact with the hand. The flexor muscle tendons of the forearm acting on the wrist, fingers and thumb exert a collective static force power many times greater, volarly, than the extensor muscle tendons acting to stabilize the same members of the wrist and hand dorsally. The ratio of these opposing forces is normally four to one. However, work demands often increase this ratio through hypertrophy of the flexor muscle tendon units by intensity and duration of tasks requiring dominantly finger, thumb, and wrist function.

Web site: http://www.delphion.com/details?pn=US06045517__

- **Gangliosides mixture, useful as a therapeutical tool for eliminating painful effects or peripheral neuropathies**

  Inventor(s): della Valle; Francesco (Padua, IT), Lorenzi; Silvana (Padua, IT), Romeo; Aurelio (Rome, IT)

  Assignee(s): Fidia, S.p.A. (Abano Terme, IT)

  Patent Number: 4,707,469

  Date filed: June 13, 1985

  Abstract: A ganglioside mixture, comprised of the gangliosides GM.sub.1, GD.sub.1a, GD.sub.1b and GT.sub.1b, has been found to possess significant analgesic or pain relieving activity. The mixture is, therefore, useful for treating pain due to various **peripheral neuropathies** and the mixture is more effective than the individual gangliosides which comprise the mixture.

  Excerpt(s): The present invention relates to a specific composition comprised of a mixture of gangliosides which mixture has been found to possess important analgesic or pain relieving activity. Gangliosides are acidic glycolipids belonging to the family of biological compounds called glycosphingolipids. They are composed of 4 basic structural units: a long-chain animoalcohol, a fatty acid, an oligosaccharide moiety and one or more sialosyl residues. The corresponding saturated compounds (sphinganines) are also present in gangliosides in minor proportions.

  Web site: http://www.delphion.com/details?pn=US04707469__

- **L-.alpha.-glycerophosphoryl-D-myo-inositol for the treatment of peripheral neuropathies and of cerebropathies**

  Inventor(s): Palazzi; Camillo M. F. G. (Palazzo Tiepolo-Segrate, IT), Procida; Carla (Palazzo Tiepolo-Segrate, IT), Scolastico; Carlo (Palazzo Tiepolo-Segrate, IT)

  Assignee(s): Apotekna S.A. (Stabio, CH)

  Patent Number: 5,281,586

  Date filed: March 2, 1992

  Abstract: Pharmaceutical compositions for the treatment of **peripheral neuropathies** of dysmetabolic or toxic origin and of cerebropathies of organic and functional origin, containing as the active ingredient L-.alpha.-glycerophosphoryl-D-myo-inosital, as such or as the alkali or alkali-earth metal salt thereof.

Excerpt(s): The present invention also relates to the alkali and alkaline-earth metal salts of GFI, particularly the calcium salt of GFI. From a chemical point of view, GFI is structurally similar to phosphatidylinositol (hereinafter called FI); FI being the double-acylated product with fatty acids, mainly unsaturated acids, at the hydroxy groups of the glycerine residue of glycerophosphorylinositol. On the contrary, GFI is the deacylated analogue and therefore it is water-soluble as such or salified, it is stable and the alkali and alkaline-earth metal salts thereof, specifically the sodium, potassium, calcium and magnesium salts, are crystalline and particularly suited for use in pharmaceutical formulations.

Web site: http://www.delphion.com/details?pn=US05281586__

- **Method of reducing or reversing neuropathy**

  Inventor(s): Hausheer; Frederick Herman (Boerne, TX)

  Assignee(s): BioNumerik Pharmaceuticals, Inc. (San Antonio, TX)

  Patent Number: 6,075,053

  Date filed: February 9, 1999

  Abstract: This invention relates to a method of treating patients afflicted with **peripheral neuropathy.** The method includes administering to a patient in need of treatment an effective amount of a thiol or reducible disulfide compound according to the formula set forth in the specification.

  Excerpt(s): This invention relates to methods of reducing or reversing neuropathy, and will have application to methods of reducing **peripheral neuropathy** which has been induced by chemotherapeutic and other agents. One of the many undesirable side effects of certain antineoplastic agents is neurotoxicity. In particular, platinum complex drugs, epipodophyllotoxins, vinca alkaloids (particularly Vincristine), taxanes, some DNA alkylating agents, antifolates, and antineoplastic antibiotics all have been known to mediate **peripheral neuropathy** in a significant percentage of patients to whom the drugs are administered. Peripheral neuropathy may also be mediated by a number of other diseases and conditions. Some of the causes include alcoholism, diabetes mellitus, certain B-vitamin deficiencies, inherited conditions, and others. Many of these neuropathies are reversible if treated promptly.

  Web site: http://www.delphion.com/details?pn=US06075053__

- **Method of treating peripheral neuropathies of the feet and legs**

  Inventor(s): Mann; Richard H. (2047 SW. 36th Ave., Delray Beach, FL 33445)

  Assignee(s): none reported

  Patent Number: 5,665,360

  Date filed: September 15, 1995

  Abstract: Peripheral neuropathies associated with Diabetes Mellitus and infection with the AIDS virus may be treated effectively by the periodic topical application of a composition containing capsicum oleoresin as the active ingredient. The oleoresin is incorporated into a pharmaceutically acceptable carrier to form a lotion, ointment, cream or the like. When applied to the skin of the affected area at least daily, pain and burning associated with the neuropathy become reduced in severity or eliminated.

Excerpt(s): This invention relates to the use of capsicum oleoresin topical preparations for the treatment of distal **peripheral neuropathies** associated with diabetes and aquired immune deficiency syndrome (AIDS) and complex, for the relief of pain and burning sensations. Debilitating pain and burning sensations of the extremities may accompany diabetes, both insulin-dependent and non-insulin dependent, and also infection with the AIDS virus or its treatment. U.S. Pat. No. 4,313,958 issued Feb. 2, 1982 to LaHann and U.S. Pat. No. 4,486,450 issued Dec. 4, 1984 to Bernstein disclose topical preparations of capsaicin (8-methyl-N-vanillyl-6-noneanamide) for producing analgesia in certain skin disorders. Capsaicin was first extracted from the fruit of the red pepper plant and is now also produced synthetically.

Web site: http://www.delphion.com/details?pn=US05665360__

- **Method of treatment of peripheral neuropathies and central neurodegenerative diseases**

  Inventor(s): Benavides; J esus (Chatenay Malabry, FR), Ferzaz; Badia (Antony, FR), George; Pascal (Saint Arnoult en Yveline, FR), Scatton; Bernard (Villebon sur Yvette, FR)

  Assignee(s): Synthelabo (Le Plessis Robinson, FR)

  Patent Number: 5,543,421

  Date filed: October 24, 1994

  Abstract: Ifenprodil and its enantiomers are disclosed for the preparation of medicines useful for the treatment of **peripheral neuropathies** and chronic neurodegenerative diseases of the central nervous system.

  Excerpt(s): The present invention concerns the use of ifenprodil and its enantiomers for the preparation of medicines useful for the treatment of **peripheral neuropathies** and central neurodegenerative diseases. Its cerebral anti-ischemic activity has been disclosed in J. Pharmacol. Exp. Ther. 247, 1211 (1988) and in Brain Research 522, 290 (1990). Ifenprodil has undergone new pharmacological studies which have demonstrated its neurotrophic properties.

  Web site: http://www.delphion.com/details?pn=US05543421__

- **Methods for treatment of drug-induced peripheral neuropathy**

  Inventor(s): Diamond; Jack (Hamilton, CA), Foreman; Mark M. (Tustin, CA), Glasky; Alvin J. (Tustin, CA)

  Assignee(s): NeoTherapeutics, Inc. (Irvine, CA)

  Patent Number: 6,630,478

  Date filed: July 6, 2001

  Abstract: A method of treating drug-induced **peripheral neuropathy** comprising administering to a patient with drug-induced **peripheral neuropathy** an effective quantity of N-4-carboxaphenyl-3-(6-oxohydropurin-9-yl)propananide AIT-082, is disclosed. Peripheral nerve sprouting can be induced through the action of a neurotrophic factor such as nerve growth factor (NGF) without the occurrence of hyperalgesia. The peripheral nerve sprouting can be nociceptive nerve sprouting. The drug-induced **peripheral neuropathy** is associated with the administration of oncolytic drugs, such as a vinca alkaloid, cisplatin, paclitaxel, suramin, altretamine, carboplatin,

chlorambucil, cytarabine, dacarbazine, docetaxel, etoposide, fludarabine, ifosfamide with mesna, tamoxifen, teniposide, or thioguanine.

Excerpt(s): This invention is directed to methods for treatment of drug-induced **peripheral neuropathy** and related conditions, particularly drug-induced **peripheral neuropathy** associated with the administration of oncolytic drugs. Many oncolytic or antineoplastic drugs have been developed in recent years. Although such drugs have proven effective in many cases in the treatment of malignancies, they can have severe side effects. One of the most serious and clinically significant side effect is **peripheral neuropathy.** Many antineoplastic drugs can cause **peripheral neuropathy.** For some of the most effective drugs, neurotoxicity is dose-limiting. It can force the termination of otherwise successful therapy, or can preclude the repetition of successful therapy. Sensory abnormalities produced by the administration of antineoplastic drugs can range from mild paresthesiae or dysesthesiae to severe neuropathic pain. In some cases, sensory and motor symptoms resolve within days or weeks after the agents are discontinued. However, **peripheral neuropathy** can be a chronic painful and disabling condition. The mechanisms that produce **peripheral neuropathy** as a consequence of the administration of oncolytic drugs are largely unknown (R. C. Polomano & G. J. Bennett, "Chemotherapy-evoked Painful **Peripheral Neuropathy,**" Pain Med. 2: 8-14 (2001); S. De Santis et al., "Patients Treated with Antitumor Drugs Displaying Neurological Deficits Are Characterized by a Low Circulating Level of Nerve Growth Factor," Clin. Cancer Res. 6: 90-95 (2000); K. Hayakawa et al., "NGF Prevention of Neurotoxicity Induced by Cisplatin, Vincristine and Taxol Depends on Toxicity of Each Drug and NGF Treatment Schedule: In Vitro Study of Adult Rat Sympathetic Ganglion Explants," Brain Res. 794: 313-319 (1998)). Accordingly, there is a need for more efficient methods of combating drug-induced **peripheral neuropathy,** particularly **peripheral neuropathy** induced by the administration of oncolytic drugs. Preferably, such methods should not interfere with cancer treatment or block the activity of the oncolytic drugs. Such methods should also not induce other side effects and should be well tolerated by cancer patients. Preferably, such methods should also combat **peripheral neuropathy** for all oncolytic drugs and should not depend on specific interactions with each individual oncolytic drug. There is a particular need for methods that can stimulate nerve growth or regeneration, particularly without inducing hyperalgesia.

Web site: http://www.delphion.com/details?pn=US06630478__

- **Nerve cell differentiation promoter**

  Inventor(s): Komagata; Daisuke (Tokyo, JP), Morino; Tomio (Oumiya, JP)

  Assignee(s): Nippon Kayaku Kabushiki Kaisha (Tokyo, JP)

  Patent Number: 5,804,186

  Date filed: November 13, 1996

  Abstract: A nerve cell differentiation promoter which comprises a physiologically active substance NK175203 or a pharmacologically acceptable salt thereof as an active ingredient is provided. It is expected that the nerve cell differentiation promoter of the present invention is applicable to a medicine for dementia, a nerve cell protective medicine or a medicine for **peripheral neuropathy** caused by anticancer agents.

  Excerpt(s): The present invention relates to a novel nerve cell differentiation promoter which comprises a physiologically active substance NK175203 or a pharmacologically acceptable salt thereof as an active ingredient and which is expected to be usable as, for

example, a medicine for dementia, a nerve cell protective medicine or a medicine for **peripheral neuropathy.** The physiologically active substance NK175203 is a publicly known compound described in International Patent Publication No. W094/05679. It is reported that this compound has an activity as a bone marrow cell proliferation promoter.

Web site: http://www.delphion.com/details?pn=US05804186__

- **Prevention and treatment of peripheral neuropathy**

  Inventor(s): Apfel; Stuart C. (218 Walker Pl., West Hempstead, NY 11552), Kessler; John A. (Wing Rd., New Canaan, CT 06840), Lewis; Michael E. (1007 Saber Rd., West Chester, PA 19382)

  Assignee(s): none reported

  Patent Number: 5,420,112

  Date filed: April 16, 1993

  Abstract: The invention features a method of preventing or treating a **peripheral neuropathy** that results from a systemic disease (e.g., post-polio syndrome) or a toxic agent (e.g., a chemotherapeutic agent), and that is not caused by an abnormal insulin level in a mammal. The method involves administering a neuropathy-reducing amount of insulin-like growth factor-I (IGF-I) or insulin-like growth factor-III (IGF-III) to the mammal.

  Excerpt(s): This invention relates to using an insulin-like growth factor-I to prevent or treat **peripheral neuropathy.** Insulin like growth factor-I (IGF-I; somatomedin C) is a member of a family of structurally and functionally related polypeptides which also includes insulin, and insulin like growth factors II (IGF-II) and III (IGF-III). All of these protein factors may play a role in neuronal development and maintenance (Recio-Pinto, E., et al., 1988, Neurochem. Int. 12:397-414). In addition, there is evidence that the levels of IGF-I and IGF-II increase substantially during regeneration after sciatic nerve transection (Hansson, H. A., et al., 1986, Acta Physiol. Scand., 126:609-614). They have been shown to promote the survival of cultured sensory and sympathetic neurons (Ishii, D. N., et al., 1987, In: Insulin, IGFs and Their Receptors in the Central Nervous System, eds., Raizada, M. K., et al., Plenum Press, NY, pp. 315-348) and, in the case of IGF-I, to promote the survival of cortical neurons (Aizenman, Y., et al., 1987, Brain Res., 406:32-42). Finally, studies both in-vitro and in-vivo have demonstrated that IGF-I and IGF-II promote motor neuron survival and neurite outgrowth (Caroni, P., et al., 1990, J. Cell Biol., 110:1307- 1317). Peripheral neuropathy generally refers to a disorder that affects the peripheral nerves, most often manifested as one or a combination of motor, sensory, sensorimotor, or autonomic neural dysfunction. The wide variety of morphologies exhibited by **peripheral neuropathies** can each be uniquely attributed to an equally wide variety of causes. For instance, **peripheral neuropathies** can be genetically acquired, can result from a systemic disease, or can be induced by a toxic agent. Some toxic agents that cause neurotoxicities are therapeutic drugs, antineoplastic agents, contaminants in foods or medicinals, andenvironmental and industrial pollutants.

  Web site: http://www.delphion.com/details?pn=US05420112__

- **Use of acetyl L-carnitine in the therapeutical treatment of peripheral neuropathies**

  Inventor(s): Calvani; Menotti (Rome, IT), Mosconi; Luigi (Rome, IT)

  Assignee(s): Sigma-Tau Industrie Farmaceutiche Riunite S.p.A. (Rome, IT)

  Patent Number: 4,751,242

  Date filed: July 27, 1987

  Abstract: Oral or parenteral administration of 1,000-2,000 mg/day of acetyl L-carnitine or an equivalent amount of a pharmacologically acceptable salt thereof to patients affected by acute or chronic **peripheral neuropathy** dramatically improves their symptomatological pattern.

  Excerpt(s): The present invention relates to a novel therapeutical utilization of acetyl L-carnitine and its pharmacologically acceptable salts for the therapeutical treatment of **peripheral neuropathies.** Previous therapeutical uses of acetyl L-carnitine are already known. For instance, the U.S. Pat. No. 4,194,006, discloses the use of acetyl carnitine in the therapeutical treatment of myocardial arrhythmias and ischemias. The U.S. Pat. No. 4,343,816 discloses the use of acetyl carnitine in the therapeutical treatment of functional peripheral vascular diseases of arteries, such as Reynaud's disease and acrocyanosis. The U.S. Pat. No. 4,346,107 discloses the therapeutical effectiveness of acetyl carnitine in the treatment of patients suffering from impaired cerebral metabolism as it occurs in senile and pre-senile dementia and Alzheimer's disease. There is no relationship at all, however, between the already known therapeutical utilizations of acetyl L-carnitine and the novel utilization which is the subject matter of the present invention. This will appear more evident from the description which follows wherein a tentative biochemical explanation of acetyl L-carnitine effectiveness in **peripheral neuropathies** is illustrated.

  Web site: http://www.delphion.com/details?pn=US04751242__

- **Use of polysaccharides in acute peripheral neuropathies**

  Inventor(s): Casu; Benito (Milan, IT), Ferro; Laura (Milan, IT), Lanzarotti; Ennio (Milan, IT), Prino; Giuseppe (Milan, IT)

  Assignee(s): Crinos Industria Farmacobiologica SpA (Villa Guardia, IT)

  Patent Number: 5,605,891

  Date filed: July 21, 1993

  Abstract: Polysaccharides and more in particular glycosaminoglycans, their mixtures, fractions and derivatives thereof are effective agents in the therapy of acute **peripheral neuropathies** of traumatic and ischemic origin and in the therapy of acute **peripheral neuropathies** of toxic origin.

  Excerpt(s): This invention concerns the use of polysaccharides as effective agents in the therapy of acute **peripheral neuropathies** of traumatic and ischemic origin, as well as in the therapy of acute **peripheral neuropathies** of toxic origin. Ischemia of nerves or of nervous tissues can be induced essentially in two ways, or by intrinsic events such as vasculopathies or by extrinsic causes such as trauma, compression or injury. When ischemia affects a limb it is observed that its most distal parts are concomitantly affected by functional alterations of motor and sensor nerves. In some specific cases the onset of a mononeuropathy caused by vasculopathy can be favoured by the already weak nerve vascularization, as it happens for the peroneal nerve.

Web site: http://www.delphion.com/details?pn=US05605891__

## Patent Applications on Peripheral Neuropathy

As of December 2000, U.S. patent applications are open to public viewing.[10] Applications are patent requests which have yet to be granted. (The process to achieve a patent can take several years.) The following patent applications have been filed since December 2000 relating to peripheral neuropathy:

- **Combination treatment of multiple sclerosis (MS), other demyelinating conditions and peripheral neuropathy, especially painful neuropathies and diabetic neuropathy**

  Inventor(s): Howard, Harry R. JR.; (Bristol, CT)

  Correspondence: Pfizer Inc; 150 East 42nd Street; 5th Floor - Stop 49; New York; NY; 10017-5612; US

  Patent Application Number: 20020147206

  Date filed: December 19, 2001

  Abstract: The present invention relates to a method of treating Multiple Sclerosis, other demyelinating disorders and **peripheral neuropathy** in a mammal by administering to the mammal a neurotransmitter-inducing or precursor agent in combination with an (SRI) antidepressant or an anxiolytic agent with improvement in efficiency. It also relates to pharmaceutical compositions containing a pharmaceutically acceptable carrier, a neurotransmitter-inducing or precursor agent, and an SRI antidepressant or anxiolytic agent.

  Excerpt(s): This invention relates to a method of treating Multiple Sclerosis (MS) and other demyelinating conditions and **peripheral neuropathy** in a mammal by administering to the mammal a Serotonin Reuptake Inhibitor (SRIs) in combination with a neurotransmitter-inducing or precursor agent. It also relates to pharmaceutical compositions containing a pharmaceutically acceptable carrier, a Serotonin Reuptake Inhibitor (SRI) and a neurotransmitter-inducing or precursor agent. Multiple sclerosis is a common and well-known neurological disorder. It is characterized by episodic patches of inflammation and demyelination which can occur anywhere in the central nervous system (CNS) almost always without any involvement of the peripheral nerves. The occurrence of the patches is disseminated in time and space, hence the older alternative name of disseminated sclerosis. It is believed that the pathogenesis involves local disruption of the blood brain barrier, a local immune and inflammatory response, with consequent damage to myelin and hence to neurons. Clinically, MS can present in both sexes and at any age. However, its most common presentation is in relatively young adults often with a single focal lesion such as damage to the optic nerve (optic neuritis), an area of anesthesia or paresthesia or muscular weakness. Vertigo, nystagmus double vision, pain, incontinence, cerebellar signs, L'Hermitte's sign (paresthesia or pain in the arms and legs on flexing the neck) and a large variety of less common symptoms may occur. The initial attack is often transient and it may be weeks, months or years before a further attack occurs. Some individuals may have a stable condition, while others may have an unrelenting downhill course ending in complete paralysis. More commonly there is a long series of remissions and relapses, each relapse leaving the patient somewhat worse than before. Relapses may be triggered by stressful events or viral

[10] This has been a common practice outside the United States prior to December 2000.

infections. Elevated body temperature almost invariably makes the condition worse whereas a reduced temperature, for example induced by a cold bath, may make the condition better.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **COMPOSITIONS FOR THE TREATMENT OF PERIPHERAL NEUROPATHIES CONTAINING ANTIDEPRESSANTS AND/OR MONOAMINE OXIDASE INHIBITORS AND/OR VITAMIN B12 AND/OR PRECURSORS OR INDUCERS OF A NEUROTRANSMITTER**

  Inventor(s): WORSLEY, ANDREW PETER; (FARNBOROUGH, GB)

  Correspondence: Larson & Taylor; Transpotomac Plaza; 1199 North Fairfax Street; Suite 900; Alexandria; VA; 22314

  Patent Application Number: 20010008884

  Date filed: March 4, 1999

  Abstract: Methods and compositions for treatment of a patient suffering from a form of **peripheral neuropathy** are disclosed. The method comprises administering to the patient any one of the following combinations of components: I. A, B and C; II. A and B; III. B and C; IV. A and C, wherein A is an antidepressant or a monoamine oxidase inhibitor, B is vitamin B.sub.12, and C is a precursor or inducer of a neurotransmitter, e.g. L-phenylalanine.

  Excerpt(s): The present invention relates to the use of a combined medicament in the treatment of various forms of **peripheral neuropathy,** especially painful neuropathies and diabetic neuropathy, including diabetic amyotrophy, mononeuritis, **mononeuritis multiplex,** cranial nerve palsies and autonomic neuropathy. The invention also relates to the preparation of medicaments for such treatments. Diabetes mellitus is a metabolic disorder resulting in hyperglycaemia (raised blood sugar), polyuria (increased output of urine) and glycosuria (appearance of sugars (e.g. glucose) in the urine). Diabetes has been recognised as a major disease for centuries. In addition to defective carbohydrate metabolism, it can also lead to altered metabolism of lipids and proteins and patients are at risk of complications from microvascular and macrovascular diseases which are serious and may be fatal. Insulin dependent diabetes results from failure of the islets of Langerhans (.beta.) cells of the pancreas to produce sufficient insulin. This often arises as a result of auto-immunity directed against islet tissue. Non-insulin-dependent diabetes may in part arise from altered efficiency of insulin receptor signalling (insulin resistance) or from a relative deficiency of insulin.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Method for preventing and treating peripheral neuropathy by administering selegiline**

  Inventor(s): Bobotas, George; (Tarpon Springs, FL)

  Correspondence: Margaret J. Sampson; Vinson & Elkins Llp; 2300 First City Tower; 1001 Fannin; Austin; TX; 77002-6760; US

  Patent Application Number: 20010023260

  Date filed: May 25, 2001

Abstract: The present invention is directed to methods for alleviating the symptoms associated with **peripheral neuropathy.** The neuropathy may be the result of a genetically inherited condition, systemic disease or exposure to a toxic agent. A reduction or elimination of symptoms is obtained by administering the drug selegiline. The invention is also directed to a method for treating patients with cancer by administering a chemotherapeutic agent known to have a toxic affect on peripheral nerves together with selegiline.

Excerpt(s): The present invention relates to a medical treatment for preventing or alleviating the symptoms associated with **peripheral neuropathy** caused by disease or exposure to a toxic agent, e.g., a chemotherapeutic cytotoxic agent. A reduction or elimination of symptoms is accomplished by administering the drug selegiline. Peripheral neuropathy is associated with a wide variety of causes, including genetically acquired conditions, systemic disease or exposure to toxic agents. It can manifest itself as a dysfunction of motor, sensory, sensorimotor or autonomic nerves. Among the most important toxic agents causing **peripheral neuropathy** are therapeutic agents, particularly those used for the treatment of neoplastic disease. In certain cases, **peripheral neuropathy** is a major complication of cancer treatment and is the main factor limiting the dosage of chemotherapeutic that can be administered to a patient (Macdonald, Neurologic Clinics 9:955-967 (1991)). This is true for the commonly administered agents cisplatin, paclitaxel and vincristine (Broun, et al., Am. J. Clin. Oncol. 16:18-21 (1993); Macdonald, Neurologic Clinics 9:955-967 (1991); Casey, et al., Brain 96:69-86 (1973)). The identification of methods for preventing or alleviating dose-limiting peripheral neuropathologic side effects would allow higher, and more therapeutically effective doses of these chemotherapeutics to be administered to patients, i.e., the therapeutic efficacy of such chemotherapeutics is typically a function of dose and therefore, increasing dosage provides increased patient survival (Macdonald, Neurologic Clinics 9:955-967 (1991); Oxols, Seminars in Oncology 16, suppl. 6:22-30 (1989)).

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Method for preventing and/or treating peripheral neuropathies induced by the administration of an anticancer agent**

Inventor(s): Cavazza, Claudio; (Rome, IT), Pisano, Claudio; (Aprilia, IT), Vesci, Loredana; (Rome, IT)

Correspondence: Nixon & Vanderhye P.C.; 8th Floor; 1100 North Glebe Road; Arlington; VA; 22201-4714; US

Patent Application Number: 20030199535

Date filed: November 13, 2002

Abstract: A method for preventing and/or treating **peripheral neuropathies** induced by the administration of an anticancer agent of the family of platin compounds, taxanes, epothilone class, vinca alkaloids, said method comprising the administration in a co-ordinated manner to a subject suffering from said **peripheral neuropathies,** or expected to suffer from said **peripheral neuropathies,** an effective amount of acetyl L-carnitine or of a pharmaceutically acceptable salt thereof. In case of prevention, acetyl L-carnitine is administered to a subject, in view of the need of a treatment with an anticancer agent, immediately before or immediately after surgical removal of the tumor, but in any case before the administration of the anticancer agent. Acetyl L-carnitine can enhance the supportive effect of physiological NGF during chemotherapy-induced neuropathy, thus

avoiding the problem of the local and general side effects of the exogenous administration of NGF which are a major problem of this neuroprotective strategy.

Excerpt(s): This application is a continuation-in-part of application Ser. No. 09/769,488, which is a continuation of PCT/IT99/00242. The invention described herein relates to the use of L-carnitine and alkanoyl L-carnitines in the preparation of medicaments useful in the treatment of tumours, particularly in combination with anticancer agents. It is well-known that the use of anticancer agents in human therapy causes a large number of toxic or side effects which may be life-threatening for the patients. These complications, in fact, may lead to a reduction in the doses of the agents, and occasionally to discontinuation of the therapy itself.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Method of treating peripheral vascular diseases, peripheral neuropathies, and autonomic neuropathies**

  Inventor(s): Wood, Ralph E.; (Moundsville, WA)

  Correspondence: Pfizer INC.; Patent Department, Ms8260-1611; Eastern Point Road; Groton; CT; 06340; US

  Patent Application Number: 20030105108

  Date filed: December 19, 2002

  Abstract: A method of treating a patient suffering from peripheral vascular disease, **peripheral neuropathies,** or autonomic neuropathies by administering a cGMP PDE5 inhibitor such as sildenafil. The method is particularly applicable to patients suffering from diabetic foot ulcers, Raynaud's Phenomenon, CREST Syndrome, erythromatosis, rheumatoid diseases, diabetic retinopathies and onychiomycosis. According to the present invention, a cGMP PDE5 inhibitor may be administered as a prophylactic to patients predisposed to develop a peripheral vascular disease, **peripheral neuropathy** or autonomic neuropathy.

  Excerpt(s): This application claims the benefit of U.S. Provisional Application No. 60/215,065, filed Jun. 30, 2000, and U.S. Provisional Application No. 60/219,029, filed Jul. 18, 2000, both entitled "Method of Treating Diabetic Ulcers," the disclosures of both of which are hereby incorporated herein in their entireties. This invention relates to the use of cyclic guanosine 3', 5'-monophosphate type five (cGMP PDE5) inhibitors, including the compound sildenafil, for the treatment of disease related to peripheral vascular diseases, **peripheral neuropathies,** autonomic neuropathies, particularly the diseases which are related to diabetes. Diseases, which are related to peripheral vascular disease and autonomic neuropathies are widely varied yet consistent in their chronic pathological condition and difficulty in treatment. A large number of these diseases are related to the disease diabetes mellitus. Others, although not known to be related to diabetes are similar in their physiological effects on the peripheral vascular system. Such diseases include Raynaud's Phenomenon, including CREST syndrome, autoimmune diseases, such as erythromatosis, rheumatoid diseases, and diabetic retinopathies.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **METHODS AND COMPOSITIONS FOR TREATING OR PREVENTING PERIPHERAL NEUROPATHIES**

  Inventor(s): GALDES, ALPHONSE; (LEXINGTON, MA), MAHANTHAPPA, NAGESH; (CAMBRIDGE, MA)

  Correspondence: Ropes & Gray; One International Place; Boston; MA; 02110-2624; US

  Patent Application Number: 20030083242

  Date filed: November 6, 1998

  Abstract: The present application is directed to the discovery that hedgehog gene products are able to protect peripheral nerve cells under conditions which otherwise result in **peripheral neuropathy.** Certain aspects of the invention are directed to preparations of hedgehog polypeptides, or other molecules which regulate patched or smoothened signalling, and their uses as protective agents against both acquired and hereditary neuropathies. As used herein, "peripheral neuropathy" refers to a disorder affecting a segment of the peripheral nervous system. For instance, the method of the present invention can be used as part of a treatment program in the management of neuropathies associated with systemic disease, e.g., viral infections, diabetes, inflamation; as well as genetically acquired (hereditary) neuropathies, e.g., Charcot-Marie-Tooth disease; and neuropathies caused by a toxic agent, e.g., a chemotherapeutic agent such as vincristine.

  Excerpt(s): Conditions that affect components of a motor unit (motor neuron cells of the spinal cord, nerve, neuromuscular junction, and muscle fibers), sensory and autonomic nerves or their supportive structures are included in the broad category of "neuromuscular disorders", and include **peripheral neuropathies.** Motor nerves are responsible for voluntary movement. Their cell bodies lie within the spinal cord, and their processes transmit signals outward to specialized motor receptors on the skeletal muscles. Sensory nerves allow teh sensation of pain, vibrations or touch, and sense where limbs are positioned in space. Their cell bodies are grouped in specialized structures called sensory "ganglia" next to the spinal cord. And they transmit signals from sensory receptors in the skin and other organs inward to the central nervous system (CNS). Autonomic nerves control involuntary functions like breathing, heartbeat, blood pressure, digestion and sexual function. Their cell bodies, clustered in autonomic ganglia, are spread throughout the body. Neuropathy is a generic term used to describe diseases of the peripheral nervous system. There are about 200 known different causes of **peripheral neuropathies.** Although most neuropathies affect all three types of nerve fibers, to varying degrees, some diseases involve only one or two, and are thus said to be purely or predominantly motor, sensory, or autonomic neuropathies.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Methods for preventing and treating peripheral neuropathy by administering desmethylselegiline delivery compositions**

  Inventor(s): Blume, Cheryl D.; (Tampa, FL), DiSanto, Anthony R.; (Gobles, MI)

  Correspondence: Margaret J. Sampson; Vinson & Elkins Llp; 2300 First City Tower; 1001 Fannin; Houston; TX; 77002-6760; US

  Patent Application Number: 20030191191

  Date filed: March 4, 2003

Abstract: The present disclosure is directed to methods for alleviating the symptoms associated with **peripheral neuropathy** by administering R(-)-desmethylselegiline, S(+) desmethylselegiline, or a combination of the two. The neuropathy may be the result of a genetically inherited condition, a systemic disease, or exposure to a toxic agent. The disclosure is also directed to a method for treating patients with cancer by administering a chemotherapeutic agent known to have a toxic affect on peripheral nerves together with R(-)-desmethylselegiline, S(+) desmethylselegiline, or a mixture of the two.

Excerpt(s): Not applicable. The present invention relates to methods and pharmaceutical compositions for using the selegiline metabolite R(-)-desmethylselegiline (also referred to simply as "desmethylselegiline" or "R(-)DMS") alone; its enantiomer ent-desmethylselegiline (also referred to as "S(+) desmethylselegiline" or "S(+)DMS") alone; or a combination, such as, for example, a racemic mixture, of the two enantiomers. In particular, the present invention provides compositions and methods for using these agents to prevent or treat **peripheral neuropathy,** particularly for preventing or alleviating the symptoms associated with **peripheral neuropathy** caused by disease or exposure to a toxic agent, e.g., a chemotherapeutic agent.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Methods for treatment of disease-induced peripheral neuropathy and related conditions**

Inventor(s): Diamond, Jack; (Hamilton, CA), Glasky, Alvin J.; (Tustin, CA)

Correspondence: Oppenheimer Wolff & Donnelly Llp; Suite 3800; 2029 Century Park East; Los Angeles; CA; 90067; US

Patent Application Number: 20020055506

Date filed: July 6, 2001

Abstract: A method of treating disease-induced **peripheral neuropathy** comprises administering to a patient with disease-induced **peripheral neuropathy** an effective quantity of a purine derivative or analogue, a tetrahydroindolone derivative or analogue, or a pyrimidine derivative or analogue. If the compound is a purine derivative, the purine moiety can be guanine or hypoxanthine. The compound can induce peripheral nerve sprouting through the action of a neurotrophic factor such as nerve growth factor (NGF) without the occurrence of hyperalgesia. The peripheral nerve sprouting can be nociceptive nerve sprouting. The disease-induced **peripheral neuropathy** can be diabetic neuropathy or disease-induced **peripheral neuropathy** with another basis.

Excerpt(s): This application claims priority from Provisional Application Ser. No. 60/216,844, filed Jul. 7, 2000 by Jack Diamond and Alvin J. Glasky, and entitled "Methods for Treatment of **Peripheral Neuropathy** and Related Conditions with Bifunctional Purine Analogues," which is incorporated herein in its entirety by this reference. This invention is directed to methods for treatment of disease-induced **peripheral neuropathy** and related conditions, particularly with purine derivatives or analogues, tetrahydroindolone derivatives or analogues, or pyrimidine derivatives or analogues. Although methods have improved for the treatment of diabetes and its consequences, diabetic neuropathy is still an extremely serious problem. Diabetic neuropathy can be defined as a demonstrable disorder, either clinically evident or subclinical, that occurs in the setting of diabetes mellitus without other causes for **peripheral neuropathy.** The neuropathic disorder includes manifestations in the

somatic and/or autonomic parts of the peripheral nervous system. Diabetic neuropathy often is associated with damage to the nerves just under the skin leading to one or more of the following conditions: numbness and tingling of fingers, hands, toes, and feet; weakness in hands and feet; or pain and/or burning sensation in hands and feet. Nerve damage as the result of **peripheral neuropathy** can also lead to problems with the GI tract, heart, and sexual organs, causing indigestion, diarrhea or constipation, dizziness, bladder infections, and impotence.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Methods for treatment of drug-induced peripheral neuropathy and related conditions**

  Inventor(s): Diamond, Jack; (Hamilton, CA), Foreman, Mark M.; (Tustin, CA), Glasky, Alvin J.; (Tustin, CA)

  Correspondence: Attn: Michael B. Farber, ESQ.; Oppenheimer Wolff & Donnelly Llp; Suite 3800; 2029 Century Park East; Los Angeles; CA; 90067; US

  Patent Application Number: 20020061899

  Date filed: July 6, 2001

  Abstract: A method of treating drug-induced **peripheral neuropathy** comprises administering to a patient with drug-induced **peripheral neuropathy** an effective quantity of a purine derivative or analogue, a tetrahydroindolone derivative or analogue, or a pyrimidine derivative or analogue. If the compound is a purine derivative, the purine moiety can be guanine or hypoxanthine. The compound can induce peripheral nerve sprouting through the action of a neurotrophic factor such as nerve growth factor (NGF) without the occurrence of hyperalgesia. The peripheral nerve sprouting can be nociceptive nerve sprouting. The drug-induced **peripheral neuropathy** can be drug-induced **peripheral neuropathy** associated with the administration of oncolytic drugs, such as a vinca alkaloid, cisplatin, paclitaxel, suramin, altretamine, carboplatin, chlorambucil, cytarabine, dacarbazine, docetaxel, etoposide, fludarabine, ifosfamide with mesna, tamoxifen, teniposide, or thioguanine. Methods according to the present invention are particularly useful in treating **peripheral neuropathy** associated with the administration of vincristine, paclitaxel, or cisplatin.

  Excerpt(s): This application claims priority from Provisional Application Ser. No. 60/216,844, filed Jul. 7, 2000 by Jack Diamond and Alvin J. Glasky, and entitled "Methods for Treatment of **Peripheral Neuropathy** and Related Conditions with Bifunctional Purine Analogues," which is incorporated herein in its entirety by this reference. This invention is directed to methods for treatment of drug-induced **peripheral neuropathy** and related conditions, particularly drug-induced **peripheral neuropathy** associated with the administration of oncolytic drugs. Many oncolytic or antineoplastic drugs have been developed in recent years. Although such drugs have proven effective in many cases in the treatment of malignancies, they can have severe side effects. One of the most serious and clinically significant side effect is **peripheral neuropathy.** Many antineoplastic drugs can cause **peripheral neuropathy.** For some of the most effective drugs, neurotoxicity is dose-limiting. It can force the termination of otherwise successful therapy, or can preclude the repetition of successful therapy. Sensory abnormalities produced by the administration of antineoplastic drugs can range from mild paresthesiae or dysesthesiae to severe neuropathic pain. In some cases, sensory and motor symptoms resolve within days or weeks after the agents are discontinued. However, **peripheral neuropathy** can be a chronic painful and disabling condition. The mechanisms that produce **peripheral neuropathy** as a consequence of the

administration of oncolytic drugs are largely unknown (R. C. Polomano & G. J. Bennett, "Chemotherapy-evoked Painful **Peripheral Neuropathy,**" Pain Med. 2: 8-14 (2001); S. De Santis et al., "Patients Treated with Antitumor Drugs Displaying Neurological Deficits Are Characterized by a Low Circulating Level of Nerve Growth Factor," Clin. Cancer Res. 6: 90-95 (2000); K. Hayakawa et al., "NGF Prevention of Neurotoxicity Induced by Cisplatin, Vincristine and Taxol Depends on Toxicity of Each Drug and NGF Treatment Schedule: In Vitro Study of Adult Rat Sympathetic Ganglion Explants," Brain Res. 794: 313-319 (1998)).

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Novel human Delta3 compositions and therapeutic and diagnostic uses therefor**

  Inventor(s): Gearing, David P.; (East Doncaster, AU), McCarthy, Sean A.; (San Diego, CA)

  Correspondence: Millennium Pharmaceuticals, INC.; 75 Sidney Street; Cambridge; MA; 02139; US

  Patent Application Number: 20030180784

  Date filed: April 17, 2003

  Abstract: The invention provides nucleic acids encoding Delta3 proteins. Also provided are derivatives of Delta3 nucleic acids, polypeptides encoded thereby, and antibodies. Delta3 therapeutics, which are either antagonists or agonists of a Delta3 activity and which are capable of modulating the growth and/or differentiation of a cell, e.g., endothelial cell, are also provided herein. Furthermore, methods for treating or preventing diseases associated with an aberrant Delta3 activity and/or associated with abnormal cellular growth and/or differentiation, e.g., neurological disease or vascular disease, such as Agenesis of the Corpus Callosum with **Peripheral Neuropathy** (ACCPN), as well as diagnostic methods for detecting these diseases are disclosed.

  Excerpt(s): This application is a continuation of U.S. Ser. No. 09/568,218 filed May 9, 2000 which is a continuation-in-part of U.S. Ser. No. 08/872,855 filed Jun. 11, 1997, which is a continuation-in-part of U.S. Ser. No. 08/832,633 filed Apr. 4, 1997, abandoned, the entire contents of each of which is incorporated herein by reference. Notch, first identified in Drosophila, is the founding member of a family of transmembrane receptor proteins that mediate cell responses to intrinsic and/or extrinsic developmental cues. The cellular response to Notch signaling can be differentiation, proliferation and/or apoptosis depending on the specific developmental program. In addition to its role as a signal-transducing cell surface protein, Notch can exert its function by directly regulating gene transcription. The Notch signaling pathway comprises Notch proteins: Drosophila Notch, LIN-12 and GLP-1 in C. elegans and Notch 1-4 in mammals; ligands: Delta, Delta-1, Delta-like 1 and 3, Jagged 1 and Jagged 2 (Serrate 1 and 2 in Drosophila, respectively); intracellular effectors: CBF-1, Deltex and NF-kappa B; target genes: HES, bHLH and TLE; processing molecules: Kuzbanian; and modifiers: lunatic fringe, manic fringe, radical fringe, numb, numb-like and disheveled 1,2 3. Structural conservation of Notch family members and their ligands are seen throughout phylogeny suggesting a conserved role for this signaling pathway in various species. The product of the Delta gene, acting as a ligand, and that of the Notch gene, acting as a receptor, are key components in a lateral-inhibition signaling pathway that regulates the detailed patterning of many different tissues in Drosophila (Bray (1998) Semin Cell Dev Biol 9:591). In humans, it has recently been shown that the Notch3 gene, located on chromosome 19, is mutated in CADASIL (for cerebral

autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) patients (Joutel et al., (1996) Nature 383: 707-710). CADASIL causes a type of stroke and dementia whose key features include recurrent subcortical ischemic events, progressive vascular dementia, craniofacial paralysis, migraine and mood disorders with severe depression (Chabriat et al. (1995) Lancet 346: 934-939).

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Regulation of human substance p-like g protein-coupled receptor**

  Inventor(s): Ramakrishnan, Shyam; (Brighton, MA)

  Correspondence: Banner & Witcoff; 1001 G Street N W; Suite 1100; Washington; DC; 20001; US

  Patent Application Number: 20030104435

  Date filed: September 11, 2002

  Abstract: Reagents which regulate human substance P G protein-coupled receptor (SP-GPCR) protein and reagents which bind to human SP-GPCR gene products can play a role in preventing, ameliorating, or correcting dysfunctions or diseases including, but not limited to, urinary incontinence, inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, cluster headache, colitis, psychosis, pain, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, **peripheral neuropathy,** neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis.

  Excerpt(s): The invention relates to the area of G-protein coupled receptors. More particularly, it relates to the area of human substance P-like G protein-coupled receptor and its regulation. Many medically significant biological processes are mediated by signal transduction pathways that involve G-proteins (Lefkowitz, Nature 351, 353-354, 1991). The family of G-protein coupled receptors (GPCR) includes receptors for hormones, neurotransmitters, growth factors, and viruses. Specific examples of GPCRs include receptors for such diverse agents as dopamine, calcitonin, adrenergic hormones, endothelin, cAMP, adenosine, acetylcholine, serotonin, histamine, thrombin, kinin, follicle stimulating hormone, opsins, endothelial differentiation gene-1, rhodopsins, odorants, cytomegalovirus, G-proteins themselves, effector proteins such as phospholipase C, adenyl cyclase, and phosphodiesterase, and actuator proteins such as protein kinase A and protein kinase C. GPCRs possess seven conserved membrane-spanning domains connecting at least eight divergent hydrophilic loops. GPCRs (also known as 7TM receptors) have been characterized as including these seven conserved hydrophobic stretches of about 20 to 30 amino acids, connecting at least eight divergent hydrophilic loops. Most GPCRs have single conserved cysteine residues in each of the first two extracellular loops, which form disulfide bonds that are believed to stabilize functional protein structure. The seven transmembrane regions are designated as TM1, TM2, TM3, TM4, TM5, TM6, and TM7. TM3 has been implicated in signal transduction.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Thiazolium compounds and treatments of disorders associated with protein aging**

  Inventor(s): Egan, John J.; (New York, NY), Vasan, Sara; (New York, NY), Wagle, Dilip; (New York, NY)

  Correspondence: Dechert; P.O. Box 5218; Princeton; NJ; 08543; US

  Patent Application Number: 20020055527

  Date filed: February 23, 2001

  Abstract: A method and compositions are disclosed for, among other things, in an animal, (i) improving the elasticity or reducing wrinkles of the skin, treating (ii) diabetes or treating or preventing (iii) adverse sequelae of diabetes, (iv) kidney damage, (v) damage to blood vasculature, (vi) hypertension, (vii) retinopathy, (viii) damage to lens proteins, (ix) cataracts, (x) **peripheral neuropathy,** or (xi) osteoarthritis.

  Excerpt(s): This application claims the priority of U.S. Provisional Application No. 60/184,266 filed Feb. 23, 2000. The present invention relates, among other things, to thiazole compounds and, in an animal, (i) improving the elasticity or reducing wrinkles of the skin, treating (ii) diabetes or treating or preventing (iii) adverse sequelae of diabetes, (iv) kidney damage, (v) damage to blood vasculature, (vi) hypertension, (vii) retinopathy, (viii) damage to lens proteins, (ix) cataracts, (x) **peripheral neuropathy,** or (xi) osteoarthritis. The reaction between glucose and proteins has been known for some time. Maillard in 1912, observed that glucose or other reducing sugars react with amino acids to form adducts that undergo a series of dehydrations and rearrangements to form stable brown pigments. Further studies have suggested that stored and heat treated foods undergo nonenzymatic browning as a result of the reaction between glucose and polypeptides, resulting in cross-links and decreased bioavailability.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

## Keeping Current

In order to stay informed about patents and patent applications dealing with peripheral neuropathy, you can access the U.S. Patent Office archive via the Internet at the following Web address: **http://www.uspto.gov/patft/index.html**. You will see two broad options: (1) Issued Patent, and (2) Published Applications. To see a list of issued patents, perform the following steps: Under "Issued Patents," click "Quick Search." Then, type "peripheral neuropathy" (or synonyms) into the "Term 1" box. After clicking on the search button, scroll down to see the various patents which have been granted to date on peripheral neuropathy.

You can also use this procedure to view pending patent applications concerning peripheral neuropathy. Simply go back to **http://www.uspto.gov/patft/index.html**. Select "Quick Search" under "Published Applications." Then proceed with the steps listed above.

# CHAPTER 7. BOOKS ON PERIPHERAL NEUROPATHY

## Overview

This chapter provides bibliographic book references relating to peripheral neuropathy. In addition to online booksellers such as **www.amazon.com** and **www.bn.com**, excellent sources for book titles on peripheral neuropathy include the Combined Health Information Database and the National Library of Medicine. Your local medical library also may have these titles available for loan.

## Book Summaries: Federal Agencies

The Combined Health Information Database collects various book abstracts from a variety of healthcare institutions and federal agencies. To access these summaries, go directly to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. You will need to use the "Detailed Search" option. To find book summaries, use the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer. For the format option, select "Monograph/Book." Now type "peripheral neuropathy" (or synonyms) into the "For these words:" box. You should check back periodically with this database which is updated every three months. The following is a typical result when searching for books on peripheral neuropathy:

- **Numb Toes and Aching Soles: Coping with Peripheral Neuropathy**

  Source: San Antonio, TX: MedPress. 1999. 300 p.

  Contact: Available from MedPress. P.O. Box 691546, San Antonio, TX 78269. (888) 633-9898. Website: www.medpress.com. PRICE: $19.95 for soft back book; $29.95 for case bound book; plus shipping and handling. ISBN 0967110726.

  Summary: This book serves as a resource for people who experience pain related to peripheral neuropathy. About one half of peripheral neuropathies are related to complications from diabetes mellitus. The book focuses on traditional, conventional, and alternative treatments for neuropathic pain. The book begins with a chapter that defines peripheral neuropathy and discusses this condition in terms of its types, symptoms and effects, causes, and evaluation. The next chapter explains the physical and psychological aspects of peripheral neuropathic pain. The following chapter discusses medications for

treating peripheral neuropathic pain, including nonopioid drugs, opioids, and topical medications. A discussion of nonopioid drug costs is included. The fourth chapter focuses on other medical therapies for treating peripheral neuropathic pain, including hematologic treatments such as plasmapheresis, immunosuppressant medications, and nerve based treatments such as nerve blocks and direct nerve stimulation. This is followed by a chapter on alternative treatments, including physical therapy; psychotherapeutic methods such as relaxation and meditation training, biofeedback, self hypnosis, and prayer; hyperbaric oxygen therapy; acupuncture; touch therapies such as massage, reflexology, Reiki, Qigong, and therapeutic touch; magnets; and chelation. Treating peripheral neuropathic pain with various nutrients (vitamins A, B, C, and E; minerals such as selenium, magnesium, chromium, and zinc; and herbs such as ginkgo biloba, St. John's wart, bioflavonoids, and others) is the topic of the next chapter. In addition, the chapter provides information on other supplements such as alpha-lipoic acid, gamma linolenic acid, acetyl-L-carnitine, N-acetyl cysteine, glutamine, coenzyme Q10, S-adenosylmethionine, dimethyl sulfoxide, and methyl sulfonyl methane. The focus of the next chapter is on experimental or unapproved drugs, including aldose reductase inhibitors; aminoguanidine; COX-2; ABT-594; SNX-111; lamotrigine; memantine; natural pain relievers such as bimoclomol, cannabinoids, endorphins, and nocistatin/OFQ2; nerve regenerating compounds such as NGF, IGF-1, neutrophin-3, and GPI 1046; nimodipine; peptide T; and PN 401. This is followed by a chapter that examines diabetes and HIV. Diabetes classifications and diabetic neuropathy (types, risk factors, blood sugar control, and treatment approaches) are discussed. The final chapter presents ways of coping with peripheral neuropathy, including exercising, using heat or cold therapy, creating conducive conditions for sleeping, avoiding certain foods, and selecting appropriate footwear. The book concludes with an index.

## Book Summaries: Online Booksellers

Commercial Internet-based booksellers, such as Amazon.com and Barnes&Noble.com, offer summaries which have been supplied by each title's publisher. Some summaries also include customer reviews. Your local bookseller may have access to in-house and commercial databases that index all published books (e.g. Books in Print®). **IMPORTANT NOTE:** Online booksellers typically produce search results for medical and non-medical books. When searching for "peripheral neuropathy" at online booksellers' Web sites, you may discover non-medical books that use the generic term "peripheral neuropathy" (or a synonym) in their titles. The following is indicative of the results you might find when searching for "peripheral neuropathy" (sorted alphabetically by title; follow the hyperlink to view more details at Amazon.com):

- **Biopsy Diagnosis of Peripheral Neuropathy** by Gyl Midroni, et al; ISBN: 0750695528; http://www.amazon.com/exec/obidos/ASIN/0750695528/icongroupinterna
- **Clinical Neurophysiology Peripheral Neuropathies (Restorative Neurology, Vol 3)** by P.J. Delwaide (Editor); ISBN: 0444806938; http://www.amazon.com/exec/obidos/ASIN/0444806938/icongroupinterna
- **Emerging Opportunities in Peripheral Neuropathy: Ens Satellite Symposium, Nice, June 8, 1998** by V. Bril (Editor), G. Said (Editor) (1999); ISBN: 3805568436; http://www.amazon.com/exec/obidos/ASIN/3805568436/icongroupinterna

- **Focal Peripheral Neuropathies** by John D. Stewart, Moser Mark Stewart; ISBN: 0781717175; http://www.amazon.com/exec/obidos/ASIN/0781717175/icongroupinterna
- **Focal Peripheral Neuropathies**; ISBN: 0444011323; http://www.amazon.com/exec/obidos/ASIN/0444011323/icongroupinterna
- **International Conference on Peripheral Neuropathies** by S. Refsum; ISBN: 0444902775; http://www.amazon.com/exec/obidos/ASIN/0444902775/icongroupinterna
- **Managing peripheral neuropathy (SuDoc HE 20.3002:P 41)** by U.S. Dept of Health and Human Services; ISBN: B00010LWC4; http://www.amazon.com/exec/obidos/ASIN/B00010LWC4/icongroupinterna
- **Numb Toes and Aching Soles: Coping with Peripheral Neuropathy** by John A. Senneff; ISBN: 0967110718; http://www.amazon.com/exec/obidos/ASIN/0967110718/icongroupinterna
- **Numb Toes and Other Woes: More on Peripheral Neuropathy** by John A. Senneff (2001); ISBN: 0967110734; http://www.amazon.com/exec/obidos/ASIN/0967110734/icongroupinterna
- **Peripheral Neuropathies** by H.P. Hartung; ISBN: 0702020060; http://www.amazon.com/exec/obidos/ASIN/0702020060/icongroupinterna
- **Peripheral Neuropathies 1988: What Is Significantly New? (Fidia Research Series, Vol 21)** by J.P. Assal; ISBN: 0387971882; http://www.amazon.com/exec/obidos/ASIN/0387971882/icongroupinterna
- **Peripheral Neuropathies: Proceedings. Ed by N. Canal. Proc of Symp Held at Univ of Milan, June 26-28 (Developments in Neurology, Vol 1)** by Milan, 1 International Symposium on Peripheral Neuropathies; ISBN: 0444800794; http://www.amazon.com/exec/obidos/ASIN/0444800794/icongroupinterna
- **Peripheral Neuropathies: Report. (WHO Technical Report Series)**; ISBN: 9241206543; http://www.amazon.com/exec/obidos/ASIN/9241206543/icongroupinterna
- **Peripheral Neuropathy (100 Maxims in Neurology)** by Marinos C. Dalakas; ISBN: 0340542594; http://www.amazon.com/exec/obidos/ASIN/0340542594/icongroupinterna
- **Peripheral Neuropathy (2 Volume Set)** by Peter James Dyck (Editor), et al; ISBN: 0721632424; http://www.amazon.com/exec/obidos/ASIN/0721632424/icongroupinterna
- **Peripheral Neuropathy (International Congress Series, No 662)** by Itsuro Sobue (Editor); ISBN: 0444806210; http://www.amazon.com/exec/obidos/ASIN/0444806210/icongroupinterna
- **Peripheral Neuropathy in Childhood (International Review of Child Neurology Series)** by R.A. Ouvrier, et al; ISBN: 088167690X; http://www.amazon.com/exec/obidos/ASIN/088167690X/icongroupinterna
- **Peripheral Neuropathy: A Practical Approach to Diagnosis and Management** by Didier Cros (Editor); ISBN: 0397517815; http://www.amazon.com/exec/obidos/ASIN/0397517815/icongroupinterna
- **The Official Patient's Sourcebook on Peripheral Neuropathy: A Revised and Updated Directory for the Internet Age** by Icon Health Publications (2002); ISBN: 0597830975; http://www.amazon.com/exec/obidos/ASIN/0597830975/icongroupinterna

- **The Surgical Management of Deformities in Leprosy and Other Peripheral Neuropathies** by Noshir H. Antia, et al (1993); ISBN: 0195630580; http://www.amazon.com/exec/obidos/ASIN/0195630580/icongroupinterna

## The National Library of Medicine Book Index

The National Library of Medicine at the National Institutes of Health has a massive database of books published on healthcare and biomedicine. Go to the following Internet site, **http://locatorplus.gov/**, and then select "Search LOCATORplus." Once you are in the search area, simply type "peripheral neuropathy" (or synonyms) into the search box, and select "books only." From there, results can be sorted by publication date, author, or relevance. The following was recently catalogued by the National Library of Medicine:[11]

- **Clinical electromyography; a brief review of the electrophysiology of the motor unit and its application to the diagnosis of lower motor neuron diseases, peripheral neuropathy and the myopathies.** Author: Marinacci, Alberto Antonio,; Year: 1955; Los Angeles, San Lucas Press, 1955
- **Numb toes and aching soles: coping with peripheral neuropathy** Author: Senneff, John A.; Year: 1999; San Antonio, Tex.: MedPress, c1999; ISBN: 0967110726 http://www.amazon.com/exec/obidos/ASIN/0967110726/icongroupinterna
- **Peripheral neuropathy.** Author: Dyck, Peter James,; Year: 1984; Philadelphia: Saunders, 1984; ISBN: 0721632750 http://www.amazon.com/exec/obidos/ASIN/0721632750/icongroupinterna

## Chapters on Peripheral Neuropathy

In order to find chapters that specifically relate to peripheral neuropathy, an excellent source of abstracts is the Combined Health Information Database. You will need to limit your search to book chapters and peripheral neuropathy using the "Detailed Search" option. Go to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. To find book chapters, use the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Book Chapter." Type "peripheral neuropathy" (or synonyms) into the "For these words:" box. The following is a typical result when searching for book chapters on peripheral neuropathy:

- **Peripheral Neuropathy Pain**

  Source: in Senneff, J.A. Numb Toes and Aching Soles: Coping with Peripheral Neuropathy. San Antonio, TX: MedPress. 1999. p. 15-19.

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[11] In addition to LOCATORPlus, in collaboration with authors and publishers, the National Center for Biotechnology Information (NCBI) is currently adapting biomedical books for the Web. The books may be accessed in two ways: (1) by searching directly using any search term or phrase (in the same way as the bibliographic database PubMed), or (2) by following the links to PubMed abstracts. Each PubMed abstract has a "Books" button that displays a facsimile of the abstract in which some phrases are hypertext links. These phrases are also found in the books available at NCBI. Click on hyperlinked results in the list of books in which the phrase is found. Currently, the majority of the links are between the books and PubMed. In the future, more links will be created between the books and other types of information, such as gene and protein sequences and macromolecular structures. See **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Books**.

Contact: Available from MedPress. P.O. Box 691546, San Antonio, TX 78269. (888) 633-9898. Website: www.medpress.com. PRICE: $19.95 for soft back book; $29.95 for case bound book; plus shipping and handling. ISBN 0967110726.

Summary: This chapter focuses on the physical and psychological aspects of peripheral neuropathy (PN) pain. Although people who have PN experience many problems, the worst have to do with pain, particularly pain resulting from sensory neuropathies. There appear to be both physical and psychological components to PN pain. The physical basis is an alteration of the electrical signals that are formed by sensors in various parts of the body and transmitted through the peripheral nervous system to the brain. Alteration of the electrical signals may be the result of degeneration of the axon of the nerve cell or of the nerve cell itself or the destruction of the myelin sheath around the nerve. A recent theory about the physical basis of neuropathic pain hypothesizes that an excessive level of proteins called cytokines is a causative factor. Theories about the psychological basis of PN pain include the gate theory. The basis of this theory is that a theoretical gate in the spinal cord transmits or blocks pain signals at the brain's discretion, with positive emotions closing the gate and negative emotions opening the gate. Other researchers believe that nerve impulses giving rise to chronic pain actually travel a different pathway than does acute pain. In addition, there is speculation that there may be a relationship between a person's psychological state and the intensity of the pain experience, with stress, depression, or anxiety increasing the intensity of pain.

- **Management of Uremic Peripheral Neuropathy**

  Source: in Nissenson, A.R. and Fine, R.N., eds. Dialysis Therapy, 2nd ed. Philadelphia, PA: Hanley and Belfus, Inc. 1993. p. 277-279.

  Contact: Available from Hanley and Belfus, Inc. 210 South 13th Street, Philadelphia, PA 19107. (215) 546-7293 or (800) 426-4545. PRICE: $49.95. ISBN: 1560530588.

  Summary: This chapter, from a general medical text on dialysis therapy, considers the management of patients with uremic peripheral neuropathy. The authors note that polyneuropathy is one of the most common consequences of chronic renal failure, present in approximately two-thirds of patients beginning maintenance dialysis. Topics covered include the clinical presentation and course of uremic polyneuropathy, including the restless legs syndrome and slowing of nerve conduction velocity; and the management issues involved in this condition. The authors also comment on the positive effect that successful transplantation has on motor nerve conduction. 1 figure.

# CHAPTER 8. MULTIMEDIA ON PERIPHERAL NEUROPATHY

## Overview

In this chapter, we show you how to keep current on multimedia sources of information on peripheral neuropathy. We start with sources that have been summarized by federal agencies, and then show you how to find bibliographic information catalogued by the National Library of Medicine.

## Video Recordings

An excellent source of multimedia information on peripheral neuropathy is the Combined Health Information Database. You will need to limit your search to "Videorecording" and "peripheral neuropathy" using the "Detailed Search" option. Go directly to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. To find video productions, use the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Videorecording (videotape, videocassette, etc.)." Type "peripheral neuropathy" (or synonyms) into the "For these words:" box. The following is a typical result when searching for video recordings on peripheral neuropathy:

- **Impotence and Diabetes**

  Source: Los Angeles, CA: National Health Video, Inc. 1999. (videocassette).

  Contact: Available from National Health Video, Inc. 12021 Wilshire Blvd., Suite 550, Los Angeles, CA 90025. (800) 543-6803. Fax (310) 477-8198. E-mail: Healthvid@aol.com. PRICE: $89.00 plus shipping and handling.

  Summary: This patient education videotape program reviews the problem of erectile dysfunction (impotence) and diabetes mellitus. The program defines erectile dysfunction (ED) as the consistent inability to get and maintain an erection. The program first explores the physiology of erections (how they happen), including the need for mental and physical stimulation, nerve impulses in the brain, and responses in muscles, fibrous tissues, and veins and arteries. The program offers a diagram and the use of a balloon to describe how an erection happens, the anatomy of the corpera cavernosa, and the role of nitrous oxide as a neurochemical transmitter. Age is noted as

a factor in ED, and men with diabetes tend to develop ED 10 to 15 years earlier than men who do not have diabetes. The program notes that psychological factors (stress, depression, guilt, and performance anxiety) can cause 10 to 15 percent of ED; a series of self test questions are included for viewers to determine if psychological factors may play a role in their own ED. For men with diabetes, nerve damage (peripheral neuropathy) is the most likely culprit for causing ED; damage to the blood vessels (atherosclerosis) is another cause. Poor blood glucose control is the most important factor in both of these problems. The program includes a section noting the impact of drugs (including alcohol and nicotine) on ED. The program outlines the steps in diagnosing erectile problems, including first admitting that there is a problem, talking with a doctor, undergoing diagnostic tests, and participating in treatment. The final section reviews treatment options, reiterating the importance of good blood glucose control and describing the use of drug therapy (Viagra), vacuum erectile systems, self injection, and surgery (blood vessel repair and penile implants). The program includes drawings, graphics, and footage of patients and their physicians through the diagnosis and treatment processes.

- **Meeting the Diabetes Challenge in Long Term Care**

  Source: Cypress, CA: Medcom, Inc. 1995. (videocassette).

  Contact: Available from Medical Audio Visual Communications, Inc. P.O. Box 84548, 2336 Bloor Street West, Toronto, Ontario M6S 1TO Canada. (800) 757-4868 or (905) 602-1160. Fax (905) 602-8720. E-mail: dwc@mavc.com. PRICE: $235.00 plus shipping and handling. Order number MED307.

  Summary: This video describes the effects of diabetes on long-term care residents and presents the treatment methods used to manage this disease. Diabetes is widespread among the elderly, and it is easily overlooked because many of its symptoms are the same as those of other diseases. Treating long-term care residents who have diabetes involves balancing nutrition therapy, exercise, and medication. The video identifies the goals of nutrition therapy, discusses meal planning, and highlights the challenges posed by nutrition therapy. Other topics include diabetes pathology, exercise therapy, and medication and insulin. The video provides information on the side effects of oral hypoglycemic agents such as sulfonylureas and metformin and identifies the steps involved in monitoring residents who have diabetes. The video also describes the symptoms of acute and long-term complications of diabetes. Acute complications include hyperglycemia, hypoglycemia, ketoacidosis, and hyperosmolar syndrome. Long-term complications include microvascular and macrovascular problems and **peripheral neuropathy.** The video also offers guidelines on proper leg and foot care.

- **Feet First Video**

  Source: Harrisburg, PA: Pennsylvania Diabetes Academy. 2001. (videocassette).

  Contact: Available from Pennsylvania Diabetes Academy. 777 East Park Drive, P.O. Box 8820, Harrisburg, PA 17105-8820. (717) 558-7750 ext. 1271. Fax (717) 558-7818. E-mail: info@padiabetes.org. PRICE: $14.95.

  Summary: This videotape program is designed to encourage older people with diabetes to take an active part in their own daily foot care, in the interest of preventing foot complications. The videotape is animated with cartoon drawings, depicting older people. The program covers the physiology of cells and how both diabetes and aging can impact the circulation system, particularly that affecting the feet. The program emphasizes that proper foot care can prevent most foot and leg amputations. The

program outlines the different ways that diabetic complications, such as **peripheral neuropathy** and autonomic neuropathy, can affect the feet, causing changes in foot size and shape, and causing some reflexes to be lost, including those for hot, cold, and pain. Signs of circulation problems in the feet including cramps (particularly pain upon resting), cold feet, a pale, shiny, purple or puffy appearance, cuts and bruises that heal slowly, feet looking dry and cracked, toenails thickened or infected, and corns or callouses. The program then describes ways to prevent foot problems related to pressure, cold or hot, smoking, breaks in the skin, or infection. Viewers are encouraged to inspect their feet daily, to wear clean socks, to test water temperatures before bathing feet, to treat corns and callouses, to properly care for toenails, and to wear shoes that fit. The program concludes with a list of what not to do.

- **Smoking and Diabetes**

  Source: Los Angeles, CA: National Health Video, Inc. 1998. (videocassette).

  Contact: Available from National Health Video, Inc. 12021 Wilshire Blvd., Suite 550, Los Angeles, CA 90025. (800) 543-6803. Fax (310) 477-8198. E-mail: Healthvid@aol.com. PRICE: $89.00 plus shipping and handling. Order number 272.

  Summary: This videotape provides people who have diabetes with information on the effect of smoking on the disease. Smoking has a greater adverse effect on people who have diabetes than on otherwise healthy smokers. For example, the risk of heart disease is 14 times higher in a person has diabetes and smokes. In addition, vasoconstriction can lead to blindness and severe **peripheral neuropathy.** Other adverse effects of smoking in a person with diabetes include increasing the risk of high blood pressure, stroke, respiratory disease, various cancers, and periodontal disease; impeding the control of infection; limiting joint mobility; and contributing to impotence. The video offers tips on quitting, including learning about smoking habits and using a substitute for smoking when a pattern is identified, setting a quitting date, and using nicotine replacement therapy. In addition, the video presents suggestions on avoiding postcessation weight gain.

## Audio Recordings

The Combined Health Information Database contains abstracts on audio productions. To search CHID, go directly to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. To find audio productions, use the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Sound Recordings." Type "peripheral neuropathy" (or synonyms) into the "For these words:" box. The following is a typical result when searching for sound recordings on peripheral neuropathy:

- **Serving Individuals with Diabetes who are Blind or Visually Impaired: A Resource Guide for Vocational Rehabilitation Counselors**

  Source: Mississippi State, MS: Rehabilitation Research and Training Center on Blindness and Low Vision, Mississippi State University. 1997. 227 p.

  Contact: Available from Rehabilitation Research and Training Center on Blindness and Low Vision, Mississippi State University. Publications Manager, P.O. Drawer 6189, Mississippi State, MS 39762. (601) 325-2001 or (601) 325-8693. Fax (601) 325-8989. TDD (601) 325-8693. PRICE: $25.00 in any format.

Summary: This resource guide is designed to help counselors better serve individuals with diabetes who are blind or visually impaired. The guide refers readers to a large collection of resources on various diabetes publications, medications, and appliances. Five sections cover an introduction to diabetes; self management; current medical issues; employment issues; and emotional aspects of diabetes. Topics include myths about diabetes; diabetic eye disease; new nutrition guidelines for diabetes management; oral diabetes medications; diabetes and medications; insulin and measurement devices and systems; maintaining the proper temperature of insulin; blood glucose control; 'talking' blood glucose monitoring systems; and noninvasive glucose monitors. The authors also discuss diabetes and the feet; kidney failure, dialysis, and transplantation; pancreas transplantation; arthritis and diabetes; diabetes and yeast infections; hypoglycemia; diabetic **peripheral neuropathy;** diabetes and men's sexual health; cardiovascular health; diabetic ketoacidosis; diabetic dermopathy; diabetes and the Individualized Written Rehabilitation Program (IWRP); the use of Braille; health insurance; and scleral shells. The book's appendix includes lists of diabetes-related organizations, publications, listservs, and World Wide Web sites; sources of low-sugar products and products for the blind; and diabetes equipment and supplies, including insulin syringe magnifiers. The resource guide is available in large print, Braille, audiocassette, and computer diskette.

## Bibliography: Multimedia on Peripheral Neuropathy

The National Library of Medicine is a rich source of information on healthcare-related multimedia productions including slides, computer software, and databases. To access the multimedia database, go to the following Web site: **http://locatorplus.gov/**. Select "Search LOCATORplus." Once in the search area, simply type in peripheral neuropathy (or synonyms). Then, in the option box provided below the search box, select "Audiovisuals and Computer Files." From there, you can choose to sort results by publication date, author, or relevance. The following multimedia has been indexed on peripheral neuropathy:

- **Axonal peripheral neuropathy [videorecording]** Source: College of Medicine, Ohio State University; [produced by] Medical Audio-Visual and Television Center; Year: 1978; Format: Videorecording; Columbus, Ohio: The University: [for sale by its Health Services Audio-Visual and Television Center], c1978
- **Clinical neurochemistry and neuroimaging [videorecording]; Pain and peripheral neuropathy** Source: Stephen Salloway; Year: 1998; Format: Videorecording; [Irvine, Calif.]: CME, c1998
- **Painful peripheral neuropathies [videorecording]** Source: a Hahnemann University and Videotech Associates Inc. production; Year: 1983; Format: Videorecording; [S.l.]: The Associates, c1983
- **Peripheral neuropathies: clinical and investigative aspects [videorecording]** Source: Houston V. A. Hospital, Baylor College of Medicine with the cooperation of National Institute of Neurological and Communicative Disorders and Stroke; Year: 1976; Format: Videorecording; [Bethesda, Md.]: The Institute, 1976
- **Peripheral neuropathies [videorecording]: clinical and investigative aspects** Source: National Institute of Neurological and Communicative Disorders and Stroke; Year: 1976; Format: Videorecording; [Bethesda, Md.]: The Institute, [1976]

# CHAPTER 9. PERIODICALS AND NEWS ON PERIPHERAL NEUROPATHY

## Overview

In this chapter, we suggest a number of news sources and present various periodicals that cover peripheral neuropathy.

## News Services and Press Releases

One of the simplest ways of tracking press releases on peripheral neuropathy is to search the news wires. In the following sample of sources, we will briefly describe how to access each service. These services only post recent news intended for public viewing.

### PR Newswire

To access the PR Newswire archive, simply go to **http://www.prnewswire.com/**. Select your country. Type "peripheral neuropathy" (or synonyms) into the search box. You will automatically receive information on relevant news releases posted within the last 30 days. The search results are shown by order of relevance.

### Reuters Health

The Reuters' Medical News and Health eLine databases can be very useful in exploring news archives relating to peripheral neuropathy. While some of the listed articles are free to view, others are available for purchase for a nominal fee. To access this archive, go to **http://www.reutershealth.com/en/index.html** and search by "peripheral neuropathy" (or synonyms). The following was recently listed in this archive for peripheral neuropathy:

- **Electrical therapy relieves pain in patients with peripheral neuropathy**
  Source: Reuters Industry Breifing
  Date: February 14, 2002

- **Car mechanics may be at risk of peripheral neuropathy**
  Source: Reuters Medical News
  Date: November 15, 2001
- **Fidarestat effective for treatment of diabetic peripheral neuropathy**
  Source: Reuters Industry Breifing
  Date: October 18, 2001
- **One-legged standing can help in diagnosis of peripheral neuropathy**
  Source: Reuters Medical News
  Date: March 13, 2001
- **Simple tests screen for peripheral neuropathy in diabetic patients**
  Source: Reuters Industry Breifing
  Date: March 09, 2001
- **Capsaicin ineffective for HIV-related distal symmetrical peripheral neuropathy**
  Source: Reuters Medical News
  Date: February 10, 2000
- **Peripheral neuropathy/myopathy common side effects of HIV antiretrovirals**
  Source: Reuters Medical News
  Date: December 30, 1998
- **Simple screen detects HIV-related distal sensory peripheral neuropathy**
  Source: Reuters Medical News
  Date: December 23, 1998
- **Acupuncture and amitriptyline ineffective for HIV-related peripheral neuropathy**
  Source: Reuters Medical News
  Date: November 11, 1998
- **Statins, niacin, linked to peripheral neuropathies**
  Source: Reuters Medical News
  Date: July 20, 1998
- **Diabetic Retinopathy And Peripheral Neuropathy Not Worsened By Pregnancy**
  Source: Reuters Medical News
  Date: April 08, 1998
- **Cuba's Economic Crisis Causes Epidemic Of Optic And Peripheral Neuropathies**
  Source: Reuters Medical News
  Date: November 02, 1995
- **Peripheral Neuropathy An Adverse Effect Of Simvastatin Use**
  Source: Reuters Medical News
  Date: June 07, 1995

### The NIH

Within MEDLINEplus, the NIH has made an agreement with the New York Times Syndicate, the AP News Service, and Reuters to deliver news that can be browsed by the public. Search news releases at **http://www.nlm.nih.gov/medlineplus/alphanews_a.html**. MEDLINEplus allows you to browse across an alphabetical index. Or you can search by date at the following Web page: **http://www.nlm.nih.gov/medlineplus/newsbydate.html**. Often, news items are indexed by MEDLINEplus within its search engine.

### Business Wire

Business Wire is similar to PR Newswire. To access this archive, simply go to **http://www.businesswire.com/**. You can scan the news by industry category or company name.

### Market Wire

Market Wire is more focused on technology than the other wires. To browse the latest press releases by topic, such as alternative medicine, biotechnology, fitness, healthcare, legal, nutrition, and pharmaceuticals, access Market Wire's Medical/Health channel at **http://www.marketwire.com/mw/release_index?channel=MedicalHealth**. Or simply go to Market Wire's home page at **http://www.marketwire.com/mw/home**, type "peripheral neuropathy" (or synonyms) into the search box, and click on "Search News." As this service is technology oriented, you may wish to use it when searching for press releases covering diagnostic procedures or tests.

### Search Engines

Medical news is also available in the news sections of commercial Internet search engines. See the health news page at Yahoo (**http://dir.yahoo.com/Health/News_and_Media/**), or you can use this Web site's general news search page at **http://news.yahoo.com/**. Type in "peripheral neuropathy" (or synonyms). If you know the name of a company that is relevant to peripheral neuropathy, you can go to any stock trading Web site (such as **http://www.etrade.com/**) and search for the company name there. News items across various news sources are reported on indicated hyperlinks. Google offers a similar service at **http://news.google.com/**.

### BBC

Covering news from a more European perspective, the British Broadcasting Corporation (BBC) allows the public free access to their news archive located at **http://www.bbc.co.uk/**. Search by "peripheral neuropathy" (or synonyms).

## Newsletter Articles

Use the Combined Health Information Database, and limit your search criteria to "newsletter articles." Again, you will need to use the "Detailed Search" option. Go directly to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. Go to the bottom of the search page where "You may refine your search by." Select the dates and language that you prefer. For the format option, select "Newsletter Article." Type "peripheral neuropathy" (or synonyms) into the "For these words:" box. You should check back periodically with this database as it is updated every three months. The following is a typical result when searching for newsletter articles on peripheral neuropathy:

- **Rheumatic Manifestations of Diabetes Mellitus**

  Source: Bulletin on the Rheumatic Diseases. 49(5): 1-3. 2000.

Contact: Available from Arthritis Foundation. 1330 West Peachtree Street, Atlanta, GA 30309. (404) 872-7100. Fax (404) 872-9559. Website: www.arthritis.org.

Summary: This article discusses the musculoskeletal disorders that occur exclusively or predominantly in people who have diabetes. The musculoskeletal syndromes that occur in people who have diabetes may be divided into those related to increased collagen deposition resulting in limitation of normal joint function, those related to neuropathy, and other conditions. Nonenzymatic glycosylation of proteins and excessive deposition of these proteins in tissue has been proposed as an explanation for the development of syndromes related to increased collagen deposition. These syndromes include cheiroarthropathy, frozen shoulder, flexor tenosynovitis, and Dupuytren's contractures. Long term diabetes is frequently complicated by **peripheral neuropathy.** This may predispose to several musculoskeletal syndromes, including Charcot's arthropathy and reflex sympathetic dystrophy. Other syndromes that people who have arthritis may be more prone to include osteoarthritis, osteopenia, diffuse idiopathic skeletal hyperostosis, infections, gout, pseudogout, carpal tunnel syndrome, and rheumatoid arthritis. Decisions to use nonsteroidal antiinflammatory drugs and glucocorticoids to treat patients with musculoskeletal complaints must account for the presence of diabetes. 1 table. 20 references.

## Academic Periodicals covering Peripheral Neuropathy

Numerous periodicals are currently indexed within the National Library of Medicine's PubMed database that are known to publish articles relating to peripheral neuropathy. In addition to these sources, you can search for articles covering peripheral neuropathy that have been published by any of the periodicals listed in previous chapters. To find the latest studies published, go to **http://www.ncbi.nlm.nih.gov/pubmed**, type the name of the periodical into the search box, and click "Go."

If you want complete details about the historical contents of a journal, you can also visit the following Web site: **http://www.ncbi.nlm.nih.gov/entrez/jrbrowser.cgi**. Here, type in the name of the journal or its abbreviation, and you will receive an index of published articles. At **http://locatorplus.gov/**, you can retrieve more indexing information on medical periodicals (e.g. the name of the publisher). Select the button "Search LOCATORplus." Then type in the name of the journal and select the advanced search option "Journal Title Search."

# CHAPTER 10. RESEARCHING MEDICATIONS

## Overview

While a number of hard copy or CD-ROM resources are available for researching medications, a more flexible method is to use Internet-based databases. Broadly speaking, there are two sources of information on approved medications: public sources and private sources. We will emphasize free-to-use public sources.

## U.S. Pharmacopeia

Because of historical investments by various organizations and the emergence of the Internet, it has become rather simple to learn about the medications recommended for peripheral neuropathy. One such source is the United States Pharmacopeia. In 1820, eleven physicians met in Washington, D.C. to establish the first compendium of standard drugs for the United States. They called this compendium the U.S. Pharmacopeia (USP). Today, the USP is a non-profit organization consisting of 800 volunteer scientists, eleven elected officials, and 400 representatives of state associations and colleges of medicine and pharmacy. The USP is located in Rockville, Maryland, and its home page is located at **http://www.usp.org/**. The USP currently provides standards for over 3,700 medications. The resulting USP DI® Advice for the Patient® can be accessed through the National Library of Medicine of the National Institutes of Health. The database is partially derived from lists of federally approved medications in the Food and Drug Administration's (FDA) Drug Approvals database, located at **http://www.fda.gov/cder/da/da.htm**.

While the FDA database is rather large and difficult to navigate, the Phamacopeia is both user-friendly and free to use. It covers more than 9,000 prescription and over-the-counter medications. To access this database, simply type the following hyperlink into your Web browser: **http://www.nlm.nih.gov/medlineplus/druginformation.html**. To view examples of a given medication (brand names, category, description, preparation, proper use, precautions, side effects, etc.), simply follow the hyperlinks indicated within the United States Pharmacopeia (USP).

Below, we have compiled a list of medications associated with peripheral neuropathy. If you would like more information on a particular medication, the provided hyperlinks will direct you to ample documentation (e.g. typical dosage, side effects, drug-interaction risks, etc.).

The following drugs have been mentioned in the Pharmacopeia and other sources as being potentially applicable to peripheral neuropathy:

**Bethanechol**

- **Systemic - U.S. Brands:** Duvoid; Urabeth; Urecholine
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202090.html

**Carbamazepine**

- **Systemic - U.S. Brands:** Atretol; Carbatrol; Epitol; Tegretol; Tegretol-XR
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202111.html

**Didanosine**

- **Systemic - U.S. Brands:** Videx
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202616.html

**Fludrocortisone**

- **Systemic - U.S. Brands:** Florinef
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202244.html

**Gabapentin**

- **Systemic - U.S. Brands:** Neurontin
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202732.html

**Metoclopramide**

- **Systemic - U.S. Brands:** Octamide; Reglan
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202364.html

**Stavudine**

- **Systemic - U.S. Brands:** Zerit
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202728.html

**Zalcitabine**

- **Systemic - U.S. Brands:** HIVID
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202652.html

## Commercial Databases

In addition to the medications listed in the USP above, a number of commercial sites are available by subscription to physicians and their institutions. Or, you may be able to access these sources from your local medical library.

### Mosby's Drug Consult™

Mosby's Drug Consult™ database (also available on CD-ROM and book format) covers 45,000 drug products including generics and international brands. It provides prescribing information, drug interactions, and patient information. Subscription information is available at the following hyperlink: **http://www.mosbysdrugconsult.com/**.

### PDR*health*

The PDR*health* database is a free-to-use, drug information search engine that has been written for the public in layman's terms. It contains FDA-approved drug information adapted from the Physicians' Desk Reference (PDR) database. PDR*health* can be searched by brand name, generic name, or indication. It features multiple drug interactions reports. Search PDR*health* at **http://www.pdrhealth.com/drug_info/index.html**.

### Other Web Sites

Drugs.com (**www.drugs.com**) reproduces the information in the Pharmacopeia as well as commercial information. You may also want to consider the Web site of the Medical Letter, Inc. (**http://www.medletter.com/**) which allows users to download articles on various drugs and therapeutics for a nominal fee.

If you have any questions about a medical treatment, the FDA may have an office near you. Look for their number in the blue pages of the phone book. You can also contact the FDA through its toll-free number, 1-888-INFO-FDA (1-888-463-6332), or on the World Wide Web at **www.fda.gov**.

# APPENDICES

# APPENDIX A. PHYSICIAN RESOURCES

## Overview

In this chapter, we focus on databases and Internet-based guidelines and information resources created or written for a professional audience.

## NIH Guidelines

Commonly referred to as "clinical" or "professional" guidelines, the National Institutes of Health publish physician guidelines for the most common diseases. Publications are available at the following by relevant Institute[12]:

- Office of the Director (OD); guidelines consolidated across agencies available at **http://www.nih.gov/health/consumer/conkey.htm**
- National Institute of General Medical Sciences (NIGMS); fact sheets available at **http://www.nigms.nih.gov/news/facts/**
- National Library of Medicine (NLM); extensive encyclopedia (A.D.A.M., Inc.) with guidelines: **http://www.nlm.nih.gov/medlineplus/healthtopics.html**
- National Cancer Institute (NCI); guidelines available at **http://www.cancer.gov/cancerinfo/list.aspx?viewid=5f35036e-5497-4d86-8c2c-714a9f7c8d25**
- National Eye Institute (NEI); guidelines available at **http://www.nei.nih.gov/order/index.htm**
- National Heart, Lung, and Blood Institute (NHLBI); guidelines available at **http://www.nhlbi.nih.gov/guidelines/index.htm**
- National Human Genome Research Institute (NHGRI); research available at **http://www.genome.gov/page.cfm?pageID=10000375**
- National Institute on Aging (NIA); guidelines available at **http://www.nia.nih.gov/health/**

[12] These publications are typically written by one or more of the various NIH Institutes.

- National Institute on Alcohol Abuse and Alcoholism (NIAAA); guidelines available at **http://www.niaaa.nih.gov/publications/publications.htm**
- National Institute of Allergy and Infectious Diseases (NIAID); guidelines available at **http://www.niaid.nih.gov/publications/**
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); fact sheets and guidelines available at **http://www.niams.nih.gov/hi/index.htm**
- National Institute of Child Health and Human Development (NICHD); guidelines available at **http://www.nichd.nih.gov/publications/pubskey.cfm**
- National Institute on Deafness and Other Communication Disorders (NIDCD); fact sheets and guidelines at **http://www.nidcd.nih.gov/health/**
- National Institute of Dental and Craniofacial Research (NIDCR); guidelines available at **http://www.nidr.nih.gov/health/**
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); guidelines available at **http://www.niddk.nih.gov/health/health.htm**
- National Institute on Drug Abuse (NIDA); guidelines available at **http://www.nida.nih.gov/DrugAbuse.html**
- National Institute of Environmental Health Sciences (NIEHS); environmental health information available at **http://www.niehs.nih.gov/external/facts.htm**
- National Institute of Mental Health (NIMH); guidelines available at **http://www.nimh.nih.gov/practitioners/index.cfm**
- National Institute of Neurological Disorders and Stroke (NINDS); neurological disorder information pages available at **http://www.ninds.nih.gov/health_and_medical/disorder_index.htm**
- National Institute of Nursing Research (NINR); publications on selected illnesses at **http://www.nih.gov/ninr/news-info/publications.html**
- National Institute of Biomedical Imaging and Bioengineering; general information at **http://grants.nih.gov/grants/becon/becon_info.htm**
- Center for Information Technology (CIT); referrals to other agencies based on keyword searches available at **http://kb.nih.gov/www_query_main.asp**
- National Center for Complementary and Alternative Medicine (NCCAM); health information available at **http://nccam.nih.gov/health/**
- National Center for Research Resources (NCRR); various information directories available at **http://www.ncrr.nih.gov/publications.asp**
- Office of Rare Diseases; various fact sheets available at **http://rarediseases.info.nih.gov/html/resources/rep_pubs.html**
- Centers for Disease Control and Prevention; various fact sheets on infectious diseases available at **http://www.cdc.gov/publications.htm**

## NIH Databases

In addition to the various Institutes of Health that publish professional guidelines, the NIH has designed a number of databases for professionals.[13] Physician-oriented resources provide a wide variety of information related to the biomedical and health sciences, both past and present. The format of these resources varies. Searchable databases, bibliographic citations, full-text articles (when available), archival collections, and images are all available. The following are referenced by the National Library of Medicine:[14]

- **Bioethics:** Access to published literature on the ethical, legal, and public policy issues surrounding healthcare and biomedical research. This information is provided in conjunction with the Kennedy Institute of Ethics located at Georgetown University, Washington, D.C.: **http://www.nlm.nih.gov/databases/databases_bioethics.html**
- **HIV/AIDS Resources:** Describes various links and databases dedicated to HIV/AIDS research: **http://www.nlm.nih.gov/pubs/factsheets/aidsinfs.html**
- **NLM Online Exhibitions:** Describes "Exhibitions in the History of Medicine": **http://www.nlm.nih.gov/exhibition/exhibition.html**. Additional resources for historical scholarship in medicine: **http://www.nlm.nih.gov/hmd/hmd.html**
- **Biotechnology Information:** Access to public databases. The National Center for Biotechnology Information conducts research in computational biology, develops software tools for analyzing genome data, and disseminates biomedical information for the better understanding of molecular processes affecting human health and disease: **http://www.ncbi.nlm.nih.gov/**
- **Population Information:** The National Library of Medicine provides access to worldwide coverage of population, family planning, and related health issues, including family planning technology and programs, fertility, and population law and policy: **http://www.nlm.nih.gov/databases/databases_population.html**
- **Cancer Information:** Access to cancer-oriented databases: **http://www.nlm.nih.gov/databases/databases_cancer.html**
- **Profiles in Science:** Offering the archival collections of prominent twentieth-century biomedical scientists to the public through modern digital technology: **http://www.profiles.nlm.nih.gov/**
- **Chemical Information:** Provides links to various chemical databases and references: **http://sis.nlm.nih.gov/Chem/ChemMain.html**
- **Clinical Alerts:** Reports the release of findings from the NIH-funded clinical trials where such release could significantly affect morbidity and mortality: **http://www.nlm.nih.gov/databases/alerts/clinical_alerts.html**
- **Space Life Sciences:** Provides links and information to space-based research (including NASA): **http://www.nlm.nih.gov/databases/databases_space.html**
- **MEDLINE:** Bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, the healthcare system, and the pre-clinical sciences: **http://www.nlm.nih.gov/databases/databases_medline.html**

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[13] Remember, for the general public, the National Library of Medicine recommends the databases referenced in MEDLINE*plus* (**http://medlineplus.gov/** or **http://www.nlm.nih.gov/medlineplus/databases.html**).

[14] See **http://www.nlm.nih.gov/databases/databases.html**.

- **Toxicology and Environmental Health Information (TOXNET):** Databases covering toxicology and environmental health: **http://sis.nlm.nih.gov/Tox/ToxMain.html**
- **Visible Human Interface:** Anatomically detailed, three-dimensional representations of normal male and female human bodies: **http://www.nlm.nih.gov/research/visible/visible_human.html**

### The Combined Health Information Database

A comprehensive source of information on clinical guidelines written for professionals is the Combined Health Information Database. You will need to limit your search to one of the following: Brochure/Pamphlet, Fact Sheet, or Information Package, and "peripheral neuropathy" using the "Detailed Search" option. Go directly to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. To find associations, use the drop boxes at the bottom of the search page where "You may refine your search by." For the publication date, select "All Years." Select your preferred language and the format option "Fact Sheet." Type "peripheral neuropathy" (or synonyms) into the "For these words:" box. The following is a sample result:

- **Thioctic Acid**

  Contact: AIDS Project Los Angeles, 3550 Wilshire Blvd Ste 300, Los Angeles, CA, 90010-2404, (213) 201-1600, http://www.apla.org.

  Summary: In this article, the author explores the potential value of thioctic acid, or lipoic acid, for the treatment of liver damage in HIV/AIDS patients. He explains that thioctic acid is a non-toxic micronutrient, incorporated by nutritional biochemists as a member of the B vitamin family, and biologically active in minute amounts. The principle physiological function of thioctic acid appears to be its action as a coenzyme in different metabolic reactions. The author states thioctic acid has been prescribed by physicians as a liver protective agent for alcoholics, and in cases of idiopathic liver enzyme elevation, viral hepatitis, and residual drug-induced liver injury. He refers to research showing thioctic acid to be effective for chemical hypersensitivity syndrome, diabetic neuropathy, **peripheral neuropathy,** heavy metal toxicity, and elevated liver enzymes. He believes thioctic acid has important implications for people with AIDS by serving to lower elevated liver enzyme levels brought on by some of their medications. Those taking thioctic acid on their own are cautioned to inform their physicians, since it will affect liver enzyme tests sometimes used to determine dosages of medications. The paper includes information on availability and prophylactic and therapeutic dosage forms.

- **The Management of Neurological Aspects of HIV Infection : A Seminar Meeting : Amsterdam, Netherlands : December 2, 1989**

  Contact: Wellcome Foundation, Group Marketing, Langley Court, Beckenham. Colwood House Medical Publications Limited, Theale Commercial Estate, 10/11 Ely Rd, Theale.

Summary: This paper highlights presentations and discussions on the management of neurological aspects of HIV infection. It describes epidemiology and the spectrum of HIV disease; pathology; management of HIV dementia; myopathy, **peripheral neuropathy,** and myelopathy; opportunistic infections and neoplasms; assessment and management of early central nervous system disorders; and antiviral therapy.

### The NLM Gateway[15]

The NLM (National Library of Medicine) Gateway is a Web-based system that lets users search simultaneously in multiple retrieval systems at the U.S. National Library of Medicine (NLM). It allows users of NLM services to initiate searches from one Web interface, providing one-stop searching for many of NLM's information resources or databases.[16] To use the NLM Gateway, simply go to the search site at **http://gateway.nlm.nih.gov/gw/Cmd**. Type "peripheral neuropathy" (or synonyms) into the search box and click "Search." The results will be presented in a tabular form, indicating the number of references in each database category.

**Results Summary**

| Category | Items Found |
|---|---|
| Journal Articles | 75757 |
| Books / Periodicals / Audio Visual | 212 |
| Consumer Health | 817 |
| Meeting Abstracts | 234 |
| Other Collections | 3 |
| Total | 77023 |

### HSTAT[17]

HSTAT is a free, Web-based resource that provides access to full-text documents used in healthcare decision-making.[18] These documents include clinical practice guidelines, quick-reference guides for clinicians, consumer health brochures, evidence reports and technology assessments from the Agency for Healthcare Research and Quality (AHRQ), as well as AHRQ's Put Prevention Into Practice.[19] Simply search by "peripheral neuropathy" (or synonyms) at the following Web site: **http://text.nlm.nih.gov**.

### Coffee Break: Tutorials for Biologists[20]

Coffee Break is a general healthcare site that takes a scientific view of the news and covers recent breakthroughs in biology that may one day assist physicians in developing treatments. Here you will find a collection of short reports on recent biological discoveries. Each report incorporates interactive tutorials that demonstrate how bioinformatics tools are

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[15] Adapted from NLM: **http://gateway.nlm.nih.gov/gw/Cmd?Overview.x**.

[16] The NLM Gateway is currently being developed by the Lister Hill National Center for Biomedical Communications (LHNCBC) at the National Library of Medicine (NLM) of the National Institutes of Health (NIH).

[17] Adapted from HSTAT: **http://www.nlm.nih.gov/pubs/factsheets/hstat.html**.

[18] The HSTAT URL is **http://hstat.nlm.nih.gov/**.

[19] Other important documents in HSTAT include: the National Institutes of Health (NIH) Consensus Conference Reports and Technology Assessment Reports; the HIV/AIDS Treatment Information Service (ATIS) resource documents; the Substance Abuse and Mental Health Services Administration's Center for Substance Abuse Treatment (SAMHSA/CSAT) Treatment Improvement Protocols (TIP) and Center for Substance Abuse Prevention (SAMHSA/CSAP) Prevention Enhancement Protocols System (PEPS); the Public Health Service (PHS) Preventive Services Task Force's *Guide to Clinical Preventive Services*; the independent, nonfederal Task Force on Community Services' *Guide to Community Preventive Services*; and the Health Technology Advisory Committee (HTAC) of the Minnesota Health Care Commission (MHCC) health technology evaluations.

[20] Adapted from **http://www.ncbi.nlm.nih.gov/Coffeebreak/Archive/FAQ.html**.

used as a part of the research process. Currently, all Coffee Breaks are written by NCBI staff.[21] Each report is about 400 words and is usually based on a discovery reported in one or more articles from recently published, peer-reviewed literature.[22] This site has new articles every few weeks, so it can be considered an online magazine of sorts. It is intended for general background information. You can access the Coffee Break Web site at the following hyperlink: **http://www.ncbi.nlm.nih.gov/Coffeebreak/**.

## Other Commercial Databases

In addition to resources maintained by official agencies, other databases exist that are commercial ventures addressing medical professionals. Here are some examples that may interest you:

- **CliniWeb International:** Index and table of contents to selected clinical information on the Internet; see **http://www.ohsu.edu/cliniweb/**.
- **Medical World Search:** Searches full text from thousands of selected medical sites on the Internet; see **http://www.mwsearch.com/**.

## The Genome Project and Peripheral Neuropathy

In the following section, we will discuss databases and references which relate to the Genome Project and peripheral neuropathy.

### Online Mendelian Inheritance in Man (OMIM)

The Online Mendelian Inheritance in Man (OMIM) database is a catalog of human genes and genetic disorders authored and edited by Dr. Victor A. McKusick and his colleagues at Johns Hopkins and elsewhere. OMIM was developed for the World Wide Web by the National Center for Biotechnology Information (NCBI).[23] The database contains textual information, pictures, and reference information. It also contains copious links to NCBI's Entrez database of MEDLINE articles and sequence information.

To search the database, go to **http://www.ncbi.nlm.nih.gov/Omim/searchomim.html**. Type "peripheral neuropathy" (or synonyms) into the search box, and click "Submit Search." If too many results appear, you can narrow the search by adding the word "clinical." Each report will have additional links to related research and databases. In particular, the option "Database Links" will search across technical databases that offer an abundance of

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[21] The figure that accompanies each article is frequently supplied by an expert external to NCBI, in which case the source of the figure is cited. The result is an interactive tutorial that tells a biological story.

[22] After a brief introduction that sets the work described into a broader context, the report focuses on how a molecular understanding can provide explanations of observed biology and lead to therapies for diseases. Each vignette is accompanied by a figure and hypertext links that lead to a series of pages that interactively show how NCBI tools and resources are used in the research process.

[23] Adapted from **http://www.ncbi.nlm.nih.gov/**. Established in 1988 as a national resource for molecular biology information, NCBI creates public databases, conducts research in computational biology, develops software tools for analyzing genome data, and disseminates biomedical information--all for the better understanding of molecular processes affecting human health and disease.

information. The following is an example of the results you can obtain from the OMIM for peripheral neuropathy:

- **Deafness, Sensorineural, with Peripheral Neuropathy and Arterial Disease**
  Web site: http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?124950
- **Optic Atrophy, Hearing Loss, and Peripheral Neuropathy**
  Web site: http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?165199
- **Peripheral Neuropathy and Optic Atrophy**
  Web site: http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?601152
- **Peripheral Neuropathy, Ataxia, Focal Necrotizing Encephalopathy, and Spongy Degeneration of Brain**
  Web site: http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?260970
- **Spinocerebellar Ataxia with Rigidity and Peripheral Neuropathy**
  Web site: http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?183050

### Genes and Disease (NCBI - Map)

The Genes and Disease database is produced by the National Center for Biotechnology Information of the National Library of Medicine at the National Institutes of Health. This Web site categorizes each disorder by system of the body. Go to **http://www.ncbi.nlm.nih.gov/disease/**, and browse the system pages to have a full view of important conditions linked to human genes. Since this site is regularly updated, you may wish to revisit it from time to time. The following systems and associated disorders are addressed:

- **Cancer:** Uncontrolled cell division.
  Examples: Breast and ovarian cancer, Burkitt lymphoma, chronic myeloid leukemia, colon cancer, lung cancer, malignant melanoma, multiple endocrine neoplasia, neurofibromatosis, p53 tumor suppressor, pancreatic cancer, prostate cancer, Ras oncogene, RB: retinoblastoma, von Hippel-Lindau syndrome.
  Web site: **http://www.ncbi.nlm.nih.gov/disease/Cancer.html**
- **Immune System:** Fights invaders.
  Examples: Asthma, autoimmune polyglandular syndrome, Crohn's disease, DiGeorge syndrome, familial Mediterranean fever, immunodeficiency with Hyper-IgM, severe combined immunodeficiency.
  Web site: **http://www.ncbi.nlm.nih.gov/disease/Immune.html**
- **Metabolism:** Food and energy.
  Examples: Adreno-leukodystrophy, atherosclerosis, Best disease, Gaucher disease, glucose galactose malabsorption, gyrate atrophy, juvenile-onset diabetes, obesity, paroxysmal nocturnal hemoglobinuria, phenylketonuria, Refsum disease, Tangier disease, Tay-Sachs disease.
  Web site: **http://www.ncbi.nlm.nih.gov/disease/Metabolism.html**
- **Muscle and Bone:** Movement and growth.
  Examples: Duchenne muscular dystrophy, Ellis-van Creveld syndrome, Marfan syndrome, myotonic dystrophy, spinal muscular atrophy.
  Web site: **http://www.ncbi.nlm.nih.gov/disease/Muscle.html**
- **Nervous System:** Mind and body.
  Examples: Alzheimer disease, amyotrophic lateral sclerosis, Angelman syndrome,

Charcot-Marie-Tooth disease, epilepsy, essential tremor, fragile X syndrome, Friedreich's ataxia, Huntington disease, Niemann-Pick disease, Parkinson disease, Prader-Willi syndrome, Rett syndrome, spinocerebellar atrophy, Williams syndrome.
Web site: **http://www.ncbi.nlm.nih.gov/disease/Brain.html**

- **Signals:** Cellular messages.
  Examples: Ataxia telangiectasia, Cockayne syndrome, glaucoma, male-patterned baldness, SRY: sex determination, tuberous sclerosis, Waardenburg syndrome, Werner syndrome.
  Web site: **http://www.ncbi.nlm.nih.gov/disease/Signals.html**
- **Transporters:** Pumps and channels.
  Examples: Cystic fibrosis, deafness, diastrophic dysplasia, Hemophilia A, long-QT syndrome, Menkes syndrome, Pendred syndrome, polycystic kidney disease, sickle cell anemia, Wilson's disease, Zellweger syndrome.
  Web site: **http://www.ncbi.nlm.nih.gov/disease/Transporters.html**

### Entrez

Entrez is a search and retrieval system that integrates several linked databases at the National Center for Biotechnology Information (NCBI). These databases include nucleotide sequences, protein sequences, macromolecular structures, whole genomes, and MEDLINE through PubMed. Entrez provides access to the following databases:

- **3D Domains:** Domains from Entrez Structure,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=geo**
- **Books:** Online books,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=books**
- **Genome:** Complete genome assemblies,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Genome**
- **NCBI's Protein Sequence Information Survey Results:**
  Web site: **http://www.ncbi.nlm.nih.gov/About/proteinsurvey/**
- **Nucleotide Sequence Database (Genbank):**
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Nucleotide**
- **OMIM:** Online Mendelian Inheritance in Man,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM**
- **PopSet:** Population study data sets,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Popset**
- **ProbeSet:** Gene Expression Omnibus (GEO),
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=geo**
- **Protein Sequence Database:**
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Protein**
- **PubMed:** Biomedical literature (PubMed),
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed**
- **Structure:** Three-dimensional macromolecular structures,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Structure**

- **Taxonomy:** Organisms in GenBank,
  Web site: **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Taxonomy**

To access the Entrez system at the National Center for Biotechnology Information, go to **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=genome**, and then select the database that you would like to search. The databases available are listed in the drop box next to "Search." Enter "peripheral neuropathy" (or synonyms) into the search box and click "Go."

### Jablonski's Multiple Congenital Anomaly/Mental Retardation (MCA/MR) Syndromes Database[24]

This online resource has been developed to facilitate the identification and differentiation of syndromic entities. Special attention is given to the type of information that is usually limited or completely omitted in existing reference sources due to space limitations of the printed form.

At **http://www.nlm.nih.gov/mesh/jablonski/syndrome_toc/toc_a.html**, you can search across syndromes using an alphabetical index**.** Search by keywords at **http://www.nlm.nih.gov/mesh/jablonski/syndrome_db.html**.

### The Genome Database[25]

Established at Johns Hopkins University in Baltimore, Maryland in 1990, the Genome Database (GDB) is the official central repository for genomic mapping data resulting from the Human Genome Initiative. In the spring of 1999, the Bioinformatics Supercomputing Centre (BiSC) at the Hospital for Sick Children in Toronto, Ontario assumed the management of GDB. The Human Genome Initiative is a worldwide research effort focusing on structural analysis of human DNA to determine the location and sequence of the estimated 100,000 human genes. In support of this project, GDB stores and curates data generated by researchers worldwide who are engaged in the mapping effort of the Human Genome Project (HGP). GDB's mission is to provide scientists with an encyclopedia of the human genome which is continually revised and updated to reflect the current state of scientific knowledge. Although GDB has historically focused on gene mapping, its focus will broaden as the Genome Project moves from mapping to sequence, and finally, to functional analysis.

To access the GDB, simply go to the following hyperlink: **http://www.gdb.org/**. Search "All Biological Data" by "Keyword." Type "peripheral neuropathy" (or synonyms) into the search box, and review the results. If more than one word is used in the search box, then separate each one with the word "and" or "or" (using "or" might be useful when using synonyms).

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[24] Adapted from the National Library of Medicine:
**http://www.nlm.nih.gov/mesh/jablonski/about_syndrome.html**.

[25] Adapted from the Genome Database: **http://gdbwww.gdb.org/gdb/aboutGDB.html - mission**.

# APPENDIX B. PATIENT RESOURCES

## Overview

Official agencies, as well as federally funded institutions supported by national grants, frequently publish a variety of guidelines written with the patient in mind. These are typically called "Fact Sheets" or "Guidelines." They can take the form of a brochure, information kit, pamphlet, or flyer. Often they are only a few pages in length. Since new guidelines on peripheral neuropathy can appear at any moment and be published by a number of sources, the best approach to finding guidelines is to systematically scan the Internet-based services that post them.

## Patient Guideline Sources

The remainder of this chapter directs you to sources which either publish or can help you find additional guidelines on topics related to peripheral neuropathy. Due to space limitations, these sources are listed in a concise manner. Do not hesitate to consult the following sources by either using the Internet hyperlink provided, or, in cases where the contact information is provided, contacting the publisher or author directly.

### The National Institutes of Health

The NIH gateway to patients is located at **http://health.nih.gov/**. From this site, you can search across various sources and institutes, a number of which are summarized below.

### Topic Pages: MEDLINEplus

The National Library of Medicine has created a vast and patient-oriented healthcare information portal called MEDLINEplus. Within this Internet-based system are "health topic pages" which list links to available materials relevant to peripheral neuropathy. To access this system, log on to **http://www.nlm.nih.gov/medlineplus/healthtopics.html**. From there you can either search using the alphabetical index or browse by broad topic areas. Recently, MEDLINEplus listed the following when searched for "peripheral neuropathy":

- Other guides

  **Charcot-Marie-Tooth Disease**
  http://www.nlm.nih.gov/medlineplus/charcotmarietoothdisease.html

  **Diabetic Nerve Problems**
  http://www.nlm.nih.gov/medlineplus/diabeticnerveproblems.html

  **Dizziness and Vertigo**
  http://www.nlm.nih.gov/medlineplus/dizzinessandvertigo.html

  **Eye Diseases**
  http://www.nlm.nih.gov/medlineplus/eyediseases.html

  **Multiple Sclerosis**
  http://www.nlm.nih.gov/medlineplus/multiplesclerosis.html

  **Neurologic Diseases**
  http://www.nlm.nih.gov/medlineplus/neurologicdiseases.html

  **Peripheral Nerve Disorders**
  http://www.nlm.nih.gov/medlineplus/peripheralnervedisorders.html

  **Vasculitis**
  http://www.nlm.nih.gov/medlineplus/vasculitis.html

  **Wegener's Granulomatosis**
  http://www.nlm.nih.gov/medlineplus/wegenersgranulomatosis.html

You may also choose to use the search utility provided by MEDLINEplus at the following Web address: **http://www.nlm.nih.gov/medlineplus/**. Simply type a keyword into the search box and click "Search." This utility is similar to the NIH search utility, with the exception that it only includes materials that are linked within the MEDLINEplus system (mostly patient-oriented information). It also has the disadvantage of generating unstructured results. We recommend, therefore, that you use this method only if you have a very targeted search.

### The Combined Health Information Database (CHID)

CHID Online is a reference tool that maintains a database directory of thousands of journal articles and patient education guidelines on peripheral neuropathy. CHID offers summaries that describe the guidelines available, including contact information and pricing. CHID's general Web site is **http://chid.nih.gov/**. To search this database, go to **http://chid.nih.gov/detail/detail.html**. In particular, you can use the advanced search options to look up pamphlets, reports, brochures, and information kits. The following was recently posted in this archive:

- **Peripheral Neuropathy**

  Contact: AIDS Treatment Data Network, 611 Broadway Ste 613, New York, NY, 10027, (212) 260-8868, http://www.atdn.org.

  Summary: This information sheet, for persons with the human immunodeficiency syndrome (HIV), explains peripheral neuropathy. The information sheet discusses peripheral neuropathy, what factors may contribute to its cause, symptoms, and treatment.

### Healthfinder™

Healthfinder™ is sponsored by the U.S. Department of Health and Human Services and offers links to hundreds of other sites that contain healthcare information. This Web site is located at **http://www.healthfinder.gov**. Again, keyword searches can be used to find guidelines. The following was recently found in this database:

- **Peripheral Neuropathy**

  Summary: A general overview of peripheral neuropathy that includes a description of the disorder, and treatment, prognosis and research information.

  Source: National Institute of Neurological Disorders and Stroke, National Institutes of Health

  http://www.healthfinder.gov/scripts/recordpass.asp?RecordType=0&RecordID=3723

### The NIH Search Utility

The NIH search utility allows you to search for documents on over 100 selected Web sites that comprise the NIH-WEB-SPACE. Each of these servers is "crawled" and indexed on an ongoing basis. Your search will produce a list of various documents, all of which will relate in some way to peripheral neuropathy. The drawbacks of this approach are that the information is not organized by theme and that the references are often a mix of information for professionals and patients. Nevertheless, a large number of the listed Web sites provide useful background information. We can only recommend this route, therefore, for relatively rare or specific disorders, or when using highly targeted searches. To use the NIH search utility, visit the following Web page: **http://search.nih.gov/index.html**.

### Additional Web Sources

A number of Web sites are available to the public that often link to government sites. These can also point you in the direction of essential information. The following is a representative sample:

- AOL: **http://search.aol.com/cat.adp?id=168&layer=&from=subcats**
- Family Village: **http://www.familyvillage.wisc.edu/specific.htm**
- Google: **http://directory.google.com/Top/Health/Conditions_and_Diseases/**
- Med Help International: **http://www.medhelp.org/HealthTopics/A.html**
- Open Directory Project: **http://dmoz.org/Health/Conditions_and_Diseases/**
- Yahoo.com: **http://dir.yahoo.com/Health/Diseases_and_Conditions/**
- WebMD®Health: **http://my.webmd.com/health_topics**

## Finding Associations

There are several Internet directories that provide lists of medical associations with information on or resources relating to peripheral neuropathy. By consulting all of

associations listed in this chapter, you will have nearly exhausted all sources for patient associations concerned with peripheral neuropathy.

### The National Health Information Center (NHIC)

The National Health Information Center (NHIC) offers a free referral service to help people find organizations that provide information about peripheral neuropathy. For more information, see the NHIC's Web site at **http://www.health.gov/NHIC/** or contact an information specialist by calling 1-800-336-4797.

### Directory of Health Organizations

The Directory of Health Organizations, provided by the National Library of Medicine Specialized Information Services, is a comprehensive source of information on associations. The Directory of Health Organizations database can be accessed via the Internet at **http://www.sis.nlm.nih.gov/Dir/DirMain.html**. It is composed of two parts: DIRLINE and Health Hotlines.

The DIRLINE database comprises some 10,000 records of organizations, research centers, and government institutes and associations that primarily focus on health and biomedicine. To access DIRLINE directly, go to the following Web site: **http://dirline.nlm.nih.gov/**. Simply type in "peripheral neuropathy" (or a synonym), and you will receive information on all relevant organizations listed in the database.

Health Hotlines directs you to toll-free numbers to over 300 organizations. You can access this database directly at **http://www.sis.nlm.nih.gov/hotlines/**. On this page, you are given the option to search by keyword or by browsing the subject list. When you have received your search results, click on the name of the organization for its description and contact information.

### The Combined Health Information Database

Another comprehensive source of information on healthcare associations is the Combined Health Information Database. Using the "Detailed Search" option, you will need to limit your search to "Organizations" and "peripheral neuropathy". Type the following hyperlink into your Web browser: **http://chid.nih.gov/detail/detail.html**. To find associations, use the drop boxes at the bottom of the search page where "You may refine your search by." For publication date, select "All Years." Then, select your preferred language and the format option "Organization Resource Sheet." Type "peripheral neuropathy" (or synonyms) into the "For these words:" box. You should check back periodically with this database since it is updated every three months.

### The National Organization for Rare Disorders, Inc.

The National Organization for Rare Disorders, Inc. has prepared a Web site that provides, at no charge, lists of associations organized by health topic. You can access this database at the following Web site: **http://www.rarediseases.org/search/orgsearch.html**. Type "peripheral neuropathy" (or a synonym) into the search box, and click "Submit Query."

# APPENDIX C. FINDING MEDICAL LIBRARIES

## Overview

In this Appendix, we show you how to quickly find a medical library in your area.

## Preparation

Your local public library and medical libraries have interlibrary loan programs with the National Library of Medicine (NLM), one of the largest medical collections in the world. According to the NLM, most of the literature in the general and historical collections of the National Library of Medicine is available on interlibrary loan to any library. If you would like to access NLM medical literature, then visit a library in your area that can request the publications for you.[26]

## Finding a Local Medical Library

The quickest method to locate medical libraries is to use the Internet-based directory published by the National Network of Libraries of Medicine (NN/LM). This network includes 4626 members and affiliates that provide many services to librarians, health professionals, and the public. To find a library in your area, simply visit **http://nnlm.gov/members/adv.html** or call 1-800-338-7657.

## Medical Libraries in the U.S. and Canada

In addition to the NN/LM, the National Library of Medicine (NLM) lists a number of libraries with reference facilities that are open to the public. The following is the NLM's list and includes hyperlinks to each library's Web site. These Web pages can provide information on hours of operation and other restrictions. The list below is a small sample of

[26] Adapted from the NLM: **http://www.nlm.nih.gov/psd/cas/interlibrary.html**.

libraries recommended by the National Library of Medicine (sorted alphabetically by name of the U.S. state or Canadian province where the library is located)[27]:

- **Alabama:** Health InfoNet of Jefferson County (Jefferson County Library Cooperative, Lister Hill Library of the Health Sciences), **http://www.uab.edu/infonet/**
- **Alabama:** Richard M. Scrushy Library (American Sports Medicine Institute)
- **Arizona:** Samaritan Regional Medical Center: The Learning Center (Samaritan Health System, Phoenix, Arizona), **http://www.samaritan.edu/library/bannerlibs.htm**
- **California:** Kris Kelly Health Information Center (St. Joseph Health System, Humboldt), **http://www.humboldt1.com/~kkhic/index.html**
- **California:** Community Health Library of Los Gatos, **http://www.healthlib.org/orgresources.html**
- **California:** Consumer Health Program and Services (CHIPS) (County of Los Angeles Public Library, Los Angeles County Harbor-UCLA Medical Center Library) - Carson, CA, **http://www.colapublib.org/services/chips.html**
- **California:** Gateway Health Library (Sutter Gould Medical Foundation)
- **California:** Health Library (Stanford University Medical Center), **http://www-med.stanford.edu/healthlibrary/**
- **California:** Patient Education Resource Center - Health Information and Resources (University of California, San Francisco), **http://sfghdean.ucsf.edu/barnett/PERC/default.asp**
- **California:** Redwood Health Library (Petaluma Health Care District), **http://www.phcd.org/rdwdlib.html**
- **California:** Los Gatos PlaneTree Health Library, **http://planetreesanjose.org/**
- **California:** Sutter Resource Library (Sutter Hospitals Foundation, Sacramento), **http://suttermedicalcenter.org/library/**
- **California:** Health Sciences Libraries (University of California, Davis), **http://www.lib.ucdavis.edu/healthsci/**
- **California:** ValleyCare Health Library & Ryan Comer Cancer Resource Center (ValleyCare Health System, Pleasanton), **http://gaelnet.stmarys-ca.edu/other.libs/gbal/east/vchl.html**
- **California:** Washington Community Health Resource Library (Fremont), **http://www.healthlibrary.org/**
- **Colorado:** William V. Gervasini Memorial Library (Exempla Healthcare), **http://www.saintjosephdenver.org/yourhealth/libraries/**
- **Connecticut:** Hartford Hospital Health Science Libraries (Hartford Hospital), **http://www.harthosp.org/library/**
- **Connecticut:** Healthnet: Connecticut Consumer Health Information Center (University of Connecticut Health Center, Lyman Maynard Stowe Library), **http://library.uchc.edu/departm/hnet/**

[27] Abstracted from **http://www.nlm.nih.gov/medlineplus/libraries.html**.

- **Connecticut:** Waterbury Hospital Health Center Library (Waterbury Hospital, Waterbury), **http://www.waterburyhospital.com/library/consumer.shtml**
- **Delaware:** Consumer Health Library (Christiana Care Health System, Eugene du Pont Preventive Medicine & Rehabilitation Institute, Wilmington), **http://www.christianacare.org/health_guide/health_guide_pmri_health_info.cfm**
- **Delaware:** Lewis B. Flinn Library (Delaware Academy of Medicine, Wilmington), **http://www.delamed.org/chls.html**
- **Georgia:** Family Resource Library (Medical College of Georgia, Augusta), **http://cmc.mcg.edu/kids_families/fam_resources/fam_res_lib/frl.htm**
- **Georgia:** Health Resource Center (Medical Center of Central Georgia, Macon), **http://www.mccg.org/hrc/hrchome.asp**
- **Hawaii:** Hawaii Medical Library: Consumer Health Information Service (Hawaii Medical Library, Honolulu), **http://hml.org/CHIS/**
- **Idaho:** DeArmond Consumer Health Library (Kootenai Medical Center, Coeur d'Alene), **http://www.nicon.org/DeArmond/index.htm**
- **Illinois:** Health Learning Center of Northwestern Memorial Hospital (Chicago), **http://www.nmh.org/health_info/hlc.html**
- **Illinois:** Medical Library (OSF Saint Francis Medical Center, Peoria), **http://www.osfsaintfrancis.org/general/library/**
- **Kentucky:** Medical Library - Services for Patients, Families, Students & the Public (Central Baptist Hospital, Lexington), **http://www.centralbap.com/education/community/library.cfm**
- **Kentucky:** University of Kentucky - Health Information Library (Chandler Medical Center, Lexington), **http://www.mc.uky.edu/PatientEd/**
- **Louisiana:** Alton Ochsner Medical Foundation Library (Alton Ochsner Medical Foundation, New Orleans), **http://www.ochsner.org/library/**
- **Louisiana:** Louisiana State University Health Sciences Center Medical Library-Shreveport, **http://lib-sh.lsuhsc.edu/**
- **Maine:** Franklin Memorial Hospital Medical Library (Franklin Memorial Hospital, Farmington), **http://www.fchn.org/fmh/lib.htm**
- **Maine:** Gerrish-True Health Sciences Library (Central Maine Medical Center, Lewiston), **http://www.cmmc.org/library/library.html**
- **Maine:** Hadley Parrot Health Science Library (Eastern Maine Healthcare, Bangor), **http://www.emh.org/hll/hpl/guide.htm**
- **Maine:** Maine Medical Center Library (Maine Medical Center, Portland), **http://www.mmc.org/library/**
- **Maine:** Parkview Hospital (Brunswick), **http://www.parkviewhospital.org/**
- **Maine:** Southern Maine Medical Center Health Sciences Library (Southern Maine Medical Center, Biddeford), **http://www.smmc.org/services/service.php3?choice=10**
- **Maine:** Stephens Memorial Hospital's Health Information Library (Western Maine Health, Norway), **http://www.wmhcc.org/Library/**

- **Manitoba, Canada:** Consumer & Patient Health Information Service (University of Manitoba Libraries), **http://www.umanitoba.ca/libraries/units/health/reference/chis.html**
- **Manitoba, Canada:** J.W. Crane Memorial Library (Deer Lodge Centre, Winnipeg), **http://www.deerlodge.mb.ca/crane_library/about.asp**
- **Maryland:** Health Information Center at the Wheaton Regional Library (Montgomery County, Dept. of Public Libraries, Wheaton Regional Library), **http://www.mont.lib.md.us/healthinfo/hic.asp**
- **Massachusetts:** Baystate Medical Center Library (Baystate Health System), **http://www.baystatehealth.com/1024/**
- **Massachusetts:** Boston University Medical Center Alumni Medical Library (Boston University Medical Center), **http://med-libwww.bu.edu/library/lib.html**
- **Massachusetts:** Lowell General Hospital Health Sciences Library (Lowell General Hospital, Lowell), **http://www.lowellgeneral.org/library/HomePageLinks/WWW.htm**
- **Massachusetts:** Paul E. Woodard Health Sciences Library (New England Baptist Hospital, Boston), **http://www.nebh.org/health_lib.asp**
- **Massachusetts:** St. Luke's Hospital Health Sciences Library (St. Luke's Hospital, Southcoast Health System, New Bedford), **http://www.southcoast.org/library/**
- **Massachusetts:** Treadwell Library Consumer Health Reference Center (Massachusetts General Hospital), **http://www.mgh.harvard.edu/library/chrcindex.html**
- **Massachusetts:** UMass HealthNet (University of Massachusetts Medical School, Worchester), **http://healthnet.umassmed.edu/**
- **Michigan:** Botsford General Hospital Library - Consumer Health (Botsford General Hospital, Library & Internet Services), **http://www.botsfordlibrary.org/consumer.htm**
- **Michigan:** Helen DeRoy Medical Library (Providence Hospital and Medical Centers), **http://www.providence-hospital.org/library/**
- **Michigan:** Marquette General Hospital - Consumer Health Library (Marquette General Hospital, Health Information Center), **http://www.mgh.org/center.html**
- **Michigan:** Patient Education Resouce Center - University of Michigan Cancer Center (University of Michigan Comprehensive Cancer Center, Ann Arbor), **http://www.cancer.med.umich.edu/learn/leares.htm**
- **Michigan:** Sladen Library & Center for Health Information Resources - Consumer Health Information (Detroit), **http://www.henryford.com/body.cfm?id=39330**
- **Montana:** Center for Health Information (St. Patrick Hospital and Health Sciences Center, Missoula)
- **National:** Consumer Health Library Directory (Medical Library Association, Consumer and Patient Health Information Section), **http://caphis.mlanet.org/directory/index.html**
- **National:** National Network of Libraries of Medicine (National Library of Medicine) - provides library services for health professionals in the United States who do not have access to a medical library, **http://nnlm.gov/**
- **National:** NN/LM List of Libraries Serving the Public (National Network of Libraries of Medicine), **http://nnlm.gov/members/**

- **Nevada:** Health Science Library, West Charleston Library (Las Vegas-Clark County Library District, Las Vegas), **http://www.lvccld.org/special_collections/medical/index.htm**
- **New Hampshire:** Dartmouth Biomedical Libraries (Dartmouth College Library, Hanover), **http://www.dartmouth.edu/~biomed/resources.htmld/conshealth.htmld/**
- **New Jersey:** Consumer Health Library (Rahway Hospital, Rahway), **http://www.rahwayhospital.com/library.htm**
- **New Jersey:** Dr. Walter Phillips Health Sciences Library (Englewood Hospital and Medical Center, Englewood), **http://www.englewoodhospital.com/links/index.htm**
- **New Jersey:** Meland Foundation (Englewood Hospital and Medical Center, Englewood), **http://www.geocities.com/ResearchTriangle/9360/**
- **New York:** Choices in Health Information (New York Public Library) - NLM Consumer Pilot Project participant, **http://www.nypl.org/branch/health/links.html**
- **New York:** Health Information Center (Upstate Medical University, State University of New York, Syracuse), **http://www.upstate.edu/library/hic/**
- **New York:** Health Sciences Library (Long Island Jewish Medical Center, New Hyde Park), **http://www.lij.edu/library/library.html**
- **New York:** ViaHealth Medical Library (Rochester General Hospital), **http://www.nyam.org/library/**
- **Ohio:** Consumer Health Library (Akron General Medical Center, Medical & Consumer Health Library), **http://www.akrongeneral.org/hwlibrary.htm**
- **Oklahoma:** The Health Information Center at Saint Francis Hospital (Saint Francis Health System, Tulsa), **http://www.sfh-tulsa.com/services/healthinfo.asp**
- **Oregon:** Planetree Health Resource Center (Mid-Columbia Medical Center, The Dalles), **http://www.mcmc.net/phrc/**
- **Pennsylvania:** Community Health Information Library (Milton S. Hershey Medical Center, Hershey), **http://www.hmc.psu.edu/commhealth/**
- **Pennsylvania:** Community Health Resource Library (Geisinger Medical Center, Danville), **http://www.geisinger.edu/education/commlib.shtml**
- **Pennsylvania:** HealthInfo Library (Moses Taylor Hospital, Scranton), **http://www.mth.org/healthwellness.html**
- **Pennsylvania:** Hopwood Library (University of Pittsburgh, Health Sciences Library System, Pittsburgh), **http://www.hsls.pitt.edu/guides/chi/hopwood/index_html**
- **Pennsylvania:** Koop Community Health Information Center (College of Physicians of Philadelphia), **http://www.collphyphil.org/kooppg1.shtml**
- **Pennsylvania:** Learning Resources Center - Medical Library (Susquehanna Health System, Williamsport), **http://www.shscares.org/services/lrc/index.asp**
- **Pennsylvania:** Medical Library (UPMC Health System, Pittsburgh), **http://www.upmc.edu/passavant/library.htm**
- **Quebec, Canada:** Medical Library (Montreal General Hospital), **http://www.mghlib.mcgill.ca/**

- **South Dakota:** Rapid City Regional Hospital Medical Library (Rapid City Regional Hospital), **http://www.rcrh.org/Services/Library/Default.asp**
- **Texas:** Houston HealthWays (Houston Academy of Medicine-Texas Medical Center Library), **http://hhw.library.tmc.edu/**
- **Washington:** Community Health Library (Kittitas Valley Community Hospital), **http://www.kvch.com/**
- **Washington:** Southwest Washington Medical Center Library (Southwest Washington Medical Center, Vancouver), **http://www.swmedicalcenter.com/body.cfm?id=72**

# ONLINE GLOSSARIES

The Internet provides access to a number of free-to-use medical dictionaries. The National Library of Medicine has compiled the following list of online dictionaries:

- ADAM Medical Encyclopedia (A.D.A.M., Inc.), comprehensive medical reference: **http://www.nlm.nih.gov/medlineplus/encyclopedia.html**
- MedicineNet.com Medical Dictionary (MedicineNet, Inc.): **http://www.medterms.com/Script/Main/hp.asp**
- Merriam-Webster Medical Dictionary (Inteli-Health, Inc.): **http://www.intelihealth.com/IH/**
- Multilingual Glossary of Technical and Popular Medical Terms in Eight European Languages (European Commission) - Danish, Dutch, English, French, German, Italian, Portuguese, and Spanish: **http://allserv.rug.ac.be/~rvdstich/eugloss/welcome.html**
- On-line Medical Dictionary (CancerWEB): **http://cancerweb.ncl.ac.uk/omd/**
- Rare Diseases Terms (Office of Rare Diseases): **http://ord.aspensys.com/asp/diseases/diseases.asp**
- Technology Glossary (National Library of Medicine) - Health Care Technology: **http://www.nlm.nih.gov/nichsr/ta101/ta10108.htm**

Beyond these, MEDLINEplus contains a very patient-friendly encyclopedia covering every aspect of medicine (licensed from A.D.A.M., Inc.). The ADAM Medical Encyclopedia can be accessed at **http://www.nlm.nih.gov/medlineplus/encyclopedia.html**. ADAM is also available on commercial Web sites such as drkoop.com (**http://www.drkoop.com/**) and Web MD (**http://my.webmd.com/adam/asset/adam_disease_articles/a_to_z/a**). The NIH suggests the following Web sites in the ADAM Medical Encyclopedia when searching for information on peripheral neuropathy:

- **Basic Guidelines for Peripheral Neuropathy**

  **Mononeuritis multiplex**
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000782.htm

  **Peripheral neuropathy**
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000593.htm

- **Signs & Symptoms for Peripheral Neuropathy**

  **Abdominal bloating**
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003123.htm

  **Abnormal sensations**
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003206.htm

  **Anhidrosis**
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003219.htm

**Bloating**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003123.htm

**Blurred vision**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003029.htm

**Constipation**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003125.htm

**Decreased sensation**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003206.htm

**Diarrhea**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003126.htm

**Difficulty beginning to urinate**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003143.htm

**Difficulty breathing**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003075.htm

**Difficulty swallowing**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003115.htm

**Dizziness**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003093.htm

**Double vision**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003029.htm

**Early satiety**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003127.htm

**Fainting**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003092.htm

**Foot pain**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003183.htm

**Heat intolerance**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003094.htm

**Hypotension**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003083.htm

**Impotence**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003164.htm

**Incontinence**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003142.htm

**Lack of muscle control**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003198.htm

**Lack of sensation**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003206.htm

**Leukemia**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/001299.htm

**Loss of movement**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003190.htm

**Loss of sensation**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003206.htm

**Loss of tissue mass**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003188.htm

**Male impotence**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003164.htm

**Movement difficulties**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003198.htm

**Movement difficulties:**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003198.htm

**Muscle**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003193.htm

**Muscle atrophy**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003188.htm

**Muscle wasting**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003188.htm

**Muscle weakness**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003174.htm

**Nausea**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003117.htm

**Numbness**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003206.htm

**Paralysis**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003190.htm

**Paresthesia**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003206.htm

**Skin ulcer**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003220.htm

**Sweating**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003218.htm

**Swelling**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003103.htm

**Tingling**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003206.htm

**Urinary hesitancy**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003143.htm

**Vomiting**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003117.htm

**Weakness**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003174.htm

**Weight loss**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003107.htm

- **Diagnostics and Tests for Peripheral Neuropathy**

**Biopsy**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003416.htm

**Blood pressure**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003398.htm

**Blood sugar levels**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003482.htm

**Blood-sugar levels**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003482.htm

**Casts**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003586.htm

**Cysts**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003240.htm

**EMG**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003929.htm

**Nerve biopsy**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003928.htm

**Nerve conduction tests**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003927.htm

**Nerve conduction velocity**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003927.htm

**Ulcer**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003225.htm

**X-ray**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003337.htm

- **Background Topics for Peripheral Neuropathy**

**Analgesics**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002123.htm

**Incidence**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002387.htm

**Mercury**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002476.htm

**Myelin**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002261.htm

**Pain medications**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002123.htm

**Peripheral**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002273.htm

**Safety**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/001931.htm

**Splints**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000040.htm

**Systemic**
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002294.htm

## Online Dictionary Directories

The following are additional online directories compiled by the National Library of Medicine, including a number of specialized medical dictionaries:

- Medical Dictionaries: Medical & Biological (World Health Organization): **http://www.who.int/hlt/virtuallibrary/English/diction.htm#Medical**
- MEL-Michigan Electronic Library List of Online Health and Medical Dictionaries (Michigan Electronic Library): **http://mel.lib.mi.us/health/health-dictionaries.html**
- Patient Education: Glossaries (DMOZ Open Directory Project): **http://dmoz.org/Health/Education/Patient_Education/Glossaries/**

- Web of Online Dictionaries (Bucknell University):
  **http://www.yourdictionary.com/diction5.html#medicine**

# PERIPHERAL NEUROPATHY DICTIONARY

The definitions below are derived from official public sources, including the National Institutes of Health [NIH] and the European Union [EU].

**Abdomen:** That portion of the body that lies between the thorax and the pelvis. [NIH]

**Abdominal:** Having to do with the abdomen, which is the part of the body between the chest and the hips that contains the pancreas, stomach, intestines, liver, gallbladder, and other organs. [NIH]

**Aberrant:** Wandering or deviating from the usual or normal course. [EU]

**Ablation:** The removal of an organ by surgery. [NIH]

**Acceptor:** A substance which, while normally not oxidized by oxygen or reduced by hydrogen, can be oxidized or reduced in presence of a substance which is itself undergoing oxidation or reduction. [NIH]

**Accommodation:** Adjustment, especially that of the eye for various distances. [EU]

**Acetylcholine:** A neurotransmitter. Acetylcholine in vertebrates is the major transmitter at neuromuscular junctions, autonomic ganglia, parasympathetic effector junctions, a subset of sympathetic effector junctions, and at many sites in the central nervous system. It is generally not used as an administered drug because it is broken down very rapidly by cholinesterases, but it is useful in some ophthalmological applications. [NIH]

**Acetylgalactosamine:** The N-acetyl derivative of galactosamine. [NIH]

**Acetylglucosamine:** The N-acetyl derivative of glucosamine. [NIH]

**Acid Phosphatase:** An enzyme that catalyzes the conversion of an orthophosphoric monoester and water to an alcohol and orthophosphate. EC 3.1.3.2. [NIH]

**Acidosis:** A pathologic condition resulting from accumulation of acid or depletion of the alkaline reserve (bicarbonate content) in the blood and body tissues, and characterized by an increase in hydrogen ion concentration. [EU]

**Acoustic:** Having to do with sound or hearing. [NIH]

**Acrocyanosis:** A condition marked by symmetrical cyanosis of the extremities, with persistent, uneven, mottled blue or red discoloration of the skin of the digits, wrists, and ankles and with profuse sweating and coldness of the digits. Called also Raynaud's sign. [EU]

**Actin:** Essential component of the cell skeleton. [NIH]

**Action Potentials:** The electric response of a nerve or muscle to its stimulation. [NIH]

**Activities of Daily Living:** The performance of the basic activities of self care, such as dressing, ambulation, eating, etc., in rehabilitation. [NIH]

**Acute leukemia:** A rapidly progressing cancer of the blood-forming tissue (bone marrow). [NIH]

**Acyl:** Chemical signal used by bacteria to communicate. [NIH]

**Adaptability:** Ability to develop some form of tolerance to conditions extremely different from those under which a living organism evolved. [NIH]

**Adenine:** A purine base and a fundamental unit of adenine nucleotides. [NIH]

**Adenoma:** A benign epithelial tumor with a glandular organization. [NIH]

**Adenosine:** A nucleoside that is composed of adenine and d-ribose. Adenosine or adenosine

derivatives play many important biological roles in addition to being components of DNA and RNA. Adenosine itself is a neurotransmitter. [NIH]

**Adenovirus:** A group of viruses that cause respiratory tract and eye infections. Adenoviruses used in gene therapy are altered to carry a specific tumor-fighting gene. [NIH]

**Adipose Tissue:** Connective tissue composed of fat cells lodged in the meshes of areolar tissue. [NIH]

**Adjustment:** The dynamic process wherein the thoughts, feelings, behavior, and biophysiological mechanisms of the individual continually change to adjust to the environment. [NIH]

**Adjuvant:** A substance which aids another, such as an auxiliary remedy; in immunology, nonspecific stimulator (e.g., BCG vaccine) of the immune response. [EU]

**Adjuvant Therapy:** Treatment given after the primary treatment to increase the chances of a cure. Adjuvant therapy may include chemotherapy, radiation therapy, or hormone therapy. [NIH]

**Adolescence:** The period of life beginning with the appearance of secondary sex characteristics and terminating with the cessation of somatic growth. The years usually referred to as adolescence lie between 13 and 18 years of age. [NIH]

**Adrenal Glands:** Paired glands situated in the retroperitoneal tissues at the superior pole of each kidney. [NIH]

**Adrenal insufficiency:** The reduced secretion of adrenal glands. [NIH]

**Adrenergic:** Activated by, characteristic of, or secreting epinephrine or substances with similar activity; the term is applied to those nerve fibres that liberate norepinephrine at a synapse when a nerve impulse passes, i.e., the sympathetic fibres. [EU]

**Adrenoleukodystrophy:** A chromosome X-linked disease. [NIH]

**Adverse Effect:** An unwanted side effect of treatment. [NIH]

**Aerobic:** In biochemistry, reactions that need oxygen to happen or happen when oxygen is present. [NIH]

**Aerobic Metabolism:** A chemical process in which oxygen is used to make energy from carbohydrates (sugars). Also known as aerobic respiration, oxidative metabolism, or cell respiration. [NIH]

**Aerobic Respiration:** A chemical process in which oxygen is used to make energy from carbohydrates (sugars). Also known as oxidative metabolism, cell respiration, or aerobic metabolism. [NIH]

**Aerosol:** A solution of a drug which can be atomized into a fine mist for inhalation therapy. [EU]

**Afferent:** Concerned with the transmission of neural impulse toward the central part of the nervous system. [NIH]

**Affinity:** 1. Inherent likeness or relationship. 2. A special attraction for a specific element, organ, or structure. 3. Chemical affinity; the force that binds atoms in molecules; the tendency of substances to combine by chemical reaction. 4. The strength of noncovalent chemical binding between two substances as measured by the dissociation constant of the complex. 5. In immunology, a thermodynamic expression of the strength of interaction between a single antigen-binding site and a single antigenic determinant (and thus of the stereochemical compatibility between them), most accurately applied to interactions among simple, uniform antigenic determinants such as haptens. Expressed as the association constant (K litres mole -1), which, owing to the heterogeneity of affinities in a population of antibody molecules of a given specificity, actually represents an average value (mean

intrinsic association constant). 6. The reciprocal of the dissociation constant. [EU]

**Affinity Chromatography:** In affinity chromatography, a ligand attached to a column binds specifically to the molecule to be purified. [NIH]

**Age of Onset:** The age or period of life at which a disease or the initial symptoms or manifestations of a disease appear in an individual. [NIH]

**Agenesis:** Lack of complete or normal development; congenital absence of an organ or part. [NIH]

**Agonist:** In anatomy, a prime mover. In pharmacology, a drug that has affinity for and stimulates physiologic activity at cell receptors normally stimulated by naturally occurring substances. [EU]

**Airways:** Tubes that carry air into and out of the lungs. [NIH]

**Alanine:** A non-essential amino acid that occurs in high levels in its free state in plasma. It is produced from pyruvate by transamination. It is involved in sugar and acid metabolism, increases immunity, and provides energy for muscle tissue, brain, and the central nervous system. [NIH]

**Albumin:** 1. Any protein that is soluble in water and moderately concentrated salt solutions and is coagulable by heat. 2. Serum albumin; the major plasma protein (approximately 60 per cent of the total), which is responsible for much of the plasma colloidal osmotic pressure and serves as a transport protein carrying large organic anions, such as fatty acids, bilirubin, and many drugs, and also carrying certain hormones, such as cortisol and thyroxine, when their specific binding globulins are saturated. Albumin is synthesized in the liver. Low serum levels occur in protein malnutrition, active inflammation and serious hepatic and renal disease. [EU]

**Aldehyde Dehydrogenase:** An enzyme that oxidizes an aldehyde in the presence of NAD+ and water to an acid and NADH. EC 1.2.1.3. Before 1978, it was classified as EC 1.1.1.70. [NIH]

**Aldose Reductase Inhibitor:** A class of drugs being studied as a way to prevent eye and nerve damage in people with diabetes. Aldose reductase is an enzyme that is normally present in the eye and in many other parts of the body. It helps change glucose (sugar) into a sugar alcohol called sorbitol. Too much sorbitol trapped in eye and nerve cells can damage these cells, leading to retinopathy and neuropathy. Drugs that prevent or slow (inhibit) the action of aldose reductase are being studied as a way to prevent or delay these complications of diabetes. [NIH]

**Algorithms:** A procedure consisting of a sequence of algebraic formulas and/or logical steps to calculate or determine a given task. [NIH]

**Alimentary:** Pertaining to food or nutritive material, or to the organs of digestion. [EU]

**Alkaline:** Having the reactions of an alkali. [EU]

**Alkaline Phosphatase:** An enzyme that catalyzes the conversion of an orthophosphoric monoester and water to an alcohol and orthophosphate. EC 3.1.3.1. [NIH]

**Alkaloid:** A member of a large group of chemicals that are made by plants and have nitrogen in them. Some alkaloids have been shown to work against cancer. [NIH]

**Alkylating Agents:** Highly reactive chemicals that introduce alkyl radicals into biologically active molecules and thereby prevent their proper functioning. Many are used as antineoplastic agents, but most are very toxic, with carcinogenic, mutagenic, teratogenic, and immunosuppressant actions. They have also been used as components in poison gases. [NIH]

**Alleles:** Mutually exclusive forms of the same gene, occupying the same locus on

homologous chromosomes, and governing the same biochemical and developmental process. [NIH]

**Alpha-1:** A protein with the property of inactivating proteolytic enzymes such as leucocyte collagenase and elastase. [NIH]

**Alpha-fetoprotein:** AFP. A protein normally produced by a developing fetus. AFP levels are usually undetectable in the blood of healthy nonpregnant adults. An elevated level of AFP suggests the presence of either a primary liver cancer or germ cell tumor. [NIH]

**Alternative medicine:** Practices not generally recognized by the medical community as standard or conventional medical approaches and used instead of standard treatments. Alternative medicine includes the taking of dietary supplements, megadose vitamins, and herbal preparations; the drinking of special teas; and practices such as massage therapy, magnet therapy, spiritual healing, and meditation. [NIH]

**Altretamine:** An alkylating agent proposed as an antineoplastic. It also acts as a chemosterilant for male houseflies and other insects. [NIH]

**Amantadine:** An antiviral that is used in the prophylactic or symptomatic treatment of Influenza A. It is also used as an antiparkinsonian agent, to treat extrapyramidal reactions, and for postherpetic neuralgia. The mechanisms of its effects in movement disorders are not well understood but probably reflect an increase in synthesis and release of dopamine, with perhaps some inhibition of dopamine uptake. [NIH]

**Amebiasis:** Infection with any of various amebae. It is an asymptomatic carrier state in most individuals, but diseases ranging from chronic, mild diarrhea to fulminant dysentery may occur. [NIH]

**Ameliorating:** A changeable condition which prevents the consequence of a failure or accident from becoming as bad as it otherwise would. [NIH]

**Amifostine:** A phosphorothioate proposed as a radiation-protective agent. It causes splenic vasodilation and may block autonomic ganglia. [NIH]

**Amine:** An organic compound containing nitrogen; any member of a group of chemical compounds formed from ammonia by replacement of one or more of the hydrogen atoms by organic (hydrocarbon) radicals. The amines are distinguished as primary, secondary, and tertiary, according to whether one, two, or three hydrogen atoms are replaced. The amines include allylamine, amylamine, ethylamine, methylamine, phenylamine, propylamine, and many other compounds. [EU]

**Amino acid:** Any organic compound containing an amino (-NH2 and a carboxyl (- COOH) group. The 20 a-amino acids listed in the accompanying table are the amino acids from which proteins are synthesized by formation of peptide bonds during ribosomal translation of messenger RNA; all except glycine, which is not optically active, have the L configuration. Other amino acids occurring in proteins, such as hydroxyproline in collagen, are formed by posttranslational enzymatic modification of amino acids residues in polypeptide chains. There are also several important amino acids, such as the neurotransmitter y-aminobutyric acid, that have no relation to proteins. Abbreviated AA. [EU]

**Amino Acid Sequence:** The order of amino acids as they occur in a polypeptide chain. This is referred to as the primary structure of proteins. It is of fundamental importance in determining protein conformation. [NIH]

**Amino Acid Substitution:** The naturally occurring or experimentally induced replacement of one or more amino acids in a protein with another. If a functionally equivalent amino acid is substituted, the protein may retain wild-type activity. Substitution may also diminish or eliminate protein function. Experimentally induced substitution is often used to study enzyme activities and binding site properties. [NIH]

**Amiodarone:** An antianginal and antiarrhythmic drug. It increases the duration of ventricular and atrial muscle action by inhibiting Na,K-activated myocardial adenosine triphosphatase. There is a resulting decrease in heart rate and in vascular resistance. [NIH]

**Amitriptyline:** Tricyclic antidepressant with anticholinergic and sedative properties. It appears to prevent the re-uptake of norepinephrine and serotonin at nerve terminals, thus potentiating the action of these neurotransmitters. Amitriptyline also appears to antaganize cholinergic and alpha-1 adrenergic responses to bioactive amines. [NIH]

**Ammonia:** A colorless alkaline gas. It is formed in the body during decomposition of organic materials during a large number of metabolically important reactions. [NIH]

**Amputation:** Surgery to remove part or all of a limb or appendage. [NIH]

**Amyloid:** A general term for a variety of different proteins that accumulate as extracellular fibrils of 7-10 nm and have common structural features, including a beta-pleated sheet conformation and the ability to bind such dyes as Congo red and thioflavine (Kandel, Schwartz, and Jessel, Principles of Neural Science, 3rd ed). [NIH]

**Amyloidosis:** A group of diseases in which protein is deposited in specific organs (localized amyloidosis) or throughout the body (systemic amyloidosis). Amyloidosis may be either primary (with no known cause) or secondary (caused by another disease, including some types of cancer). Generally, primary amyloidosis affects the nerves, skin, tongue, joints, heart, and liver; secondary amyloidosis often affects the spleen, kidneys, liver, and adrenal glands. [NIH]

**Amyotrophy:** A type of diabetic neuropathy that causes muscle weakness and wasting. [NIH]

**Anaesthesia:** Loss of feeling or sensation. Although the term is used for loss of tactile sensibility, or of any of the other senses, it is applied especially to loss of the sensation of pain, as it is induced to permit performance of surgery or other painful procedures. [EU]

**Anal:** Having to do with the anus, which is the posterior opening of the large bowel. [NIH]

**Analgesic:** An agent that alleviates pain without causing loss of consciousness. [EU]

**Analog:** In chemistry, a substance that is similar, but not identical, to another. [NIH]

**Analogous:** Resembling or similar in some respects, as in function or appearance, but not in origin or development;. [EU]

**Analytes:** A component of a test sample the presence of which has to be demonstrated. The term "analyte" includes where appropriate formed from the analyte during the analyses. [NIH]

**Anaphylatoxins:** The family of peptides C3a, C4a, C5a, and C5a des-arginine produced in the serum during complement activation. They produce smooth muscle contraction, mast cell histamine release, affect platelet aggregation, and act as mediators of the local inflammatory process. The order of anaphylatoxin activity from strongest to weakest is C5a, C3a, C4a, and C5a des-arginine. The latter is the so-called "classical" anaphylatoxin but shows no spasmogenic activity though it contains some chemotactic ability. [NIH]

**Anaplasia:** Loss of structural differentiation and useful function of neoplastic cells. [NIH]

**Anatomical:** Pertaining to anatomy, or to the structure of the organism. [EU]

**Anemia:** A reduction in the number of circulating erythrocytes or in the quantity of hemoglobin. [NIH]

**Anesthesia:** A state characterized by loss of feeling or sensation. This depression of nerve function is usually the result of pharmacologic action and is induced to allow performance of surgery or other painful procedures. [NIH]

**Anesthetics:** Agents that are capable of inducing a total or partial loss of sensation,

especially tactile sensation and pain. They may act to induce general anesthesia, in which an unconscious state is achieved, or may act locally to induce numbness or lack of sensation at a targeted site. [NIH]

**Angina:** Chest pain that originates in the heart. [NIH]

**Angiogenesis:** Blood vessel formation. Tumor angiogenesis is the growth of blood vessels from surrounding tissue to a solid tumor. This is caused by the release of chemicals by the tumor. [NIH]

**Angiogenesis inhibitor:** A substance that may prevent the formation of blood vessels. In anticancer therapy, an angiogenesis inhibitor prevents the growth of blood vessels from surrounding tissue to a solid tumor. [NIH]

**Animal model:** An animal with a disease either the same as or like a disease in humans. Animal models are used to study the development and progression of diseases and to test new treatments before they are given to humans. Animals with transplanted human cancers or other tissues are called xenograft models. [NIH]

**Anions:** Negatively charged atoms, radicals or groups of atoms which travel to the anode or positive pole during electrolysis. [NIH]

**Ankle:** That part of the lower limb directly above the foot. [NIH]

**Anomalies:** Birth defects; abnormalities. [NIH]

**Antecedent:** Existing or occurring before in time or order often with consequential effects. [EU]

**Anterograde:** Moving or extending forward; called also antegrade. [EU]

**Anthracycline:** A member of a family of anticancer drugs that are also antibiotics. [NIH]

**Antianginal:** Counteracting angina or anginal conditions. [EU]

**Antiarrhythmic:** An agent that prevents or alleviates cardiac arrhythmia. [EU]

**Antibacterial:** A substance that destroys bacteria or suppresses their growth or reproduction. [EU]

**Antibiotic:** A drug used to treat infections caused by bacteria and other microorganisms. [NIH]

**Antibodies:** Immunoglobulin molecules having a specific amino acid sequence by virtue of which they interact only with the antigen that induced their synthesis in cells of the lymphoid series (especially plasma cells), or with an antigen closely related to it. [NIH]

**Antibody:** A type of protein made by certain white blood cells in response to a foreign substance (antigen). Each antibody can bind to only a specific antigen. The purpose of this binding is to help destroy the antigen. Antibodies can work in several ways, depending on the nature of the antigen. Some antibodies destroy antigens directly. Others make it easier for white blood cells to destroy the antigen. [NIH]

**Anticholinergic:** An agent that blocks the parasympathetic nerves. Called also parasympatholytic. [EU]

**Anticoagulant:** A drug that helps prevent blood clots from forming. Also called a blood thinner. [NIH]

**Anticonvulsant:** An agent that prevents or relieves convulsions. [EU]

**Antidepressant:** A drug used to treat depression. [NIH]

**Antigen:** Any substance which is capable, under appropriate conditions, of inducing a specific immune response and of reacting with the products of that response, that is, with specific antibody or specifically sensitized T-lymphocytes, or both. Antigens may be soluble

substances, such as toxins and foreign proteins, or particulate, such as bacteria and tissue cells; however, only the portion of the protein or polysaccharide molecule known as the antigenic determinant (q.v.) combines with antibody or a specific receptor on a lymphocyte. Abbreviated Ag. [EU]

**Antigen-Antibody Complex:** The complex formed by the binding of antigen and antibody molecules. The deposition of large antigen-antibody complexes leading to tissue damage causes immune complex diseases. [NIH]

**Anti-inflammatory:** Having to do with reducing inflammation. [NIH]

**Anti-Inflammatory Agents:** Substances that reduce or suppress inflammation. [NIH]

**Antimetabolite:** A chemical that is very similar to one required in a normal biochemical reaction in cells. Antimetabolites can stop or slow down the reaction. [NIH]

**Antineoplastic:** Inhibiting or preventing the development of neoplasms, checking the maturation and proliferation of malignant cells. [EU]

**Antineoplastic Agents:** Substances that inhibit or prevent the proliferation of neoplasms. [NIH]

**Antineoplastic antibiotics:** A group of anticancer drugs that block cell growth by interfering with DNA, the genetic material in cells. Also called anticancer antibiotics or antitumor antibiotics. [NIH]

**Antioxidant:** A substance that prevents damage caused by free radicals. Free radicals are highly reactive chemicals that often contain oxygen. They are produced when molecules are split to give products that have unpaired electrons. This process is called oxidation. [NIH]

**Antiviral:** Destroying viruses or suppressing their replication. [EU]

**Anuria:** Inability to form or excrete urine. [NIH]

**Anus:** The opening of the rectum to the outside of the body. [NIH]

**Anxiety:** Persistent feeling of dread, apprehension, and impending disaster. [NIH]

**Anxiolytic:** An anxiolytic or antianxiety agent. [EU]

**Aponeurosis:** Tendinous expansion consisting of a fibrous or membranous sheath which serves as a fascia to enclose or bind a group of muscles. [NIH]

**Apoptosis:** One of the two mechanisms by which cell death occurs (the other being the pathological process of necrosis). Apoptosis is the mechanism responsible for the physiological deletion of cells and appears to be intrinsically programmed. It is characterized by distinctive morphologic changes in the nucleus and cytoplasm, chromatin cleavage at regularly spaced sites, and the endonucleolytic cleavage of genomic DNA (DNA fragmentation) at internucleosomal sites. This mode of cell death serves as a balance to mitosis in regulating the size of animal tissues and in mediating pathologic processes associated with tumor growth. [NIH]

**Aqueous:** Having to do with water. [NIH]

**Arginine:** An essential amino acid that is physiologically active in the L-form. [NIH]

**Aromatic:** Having a spicy odour. [EU]

**Arterial:** Pertaining to an artery or to the arteries. [EU]

**Arteries:** The vessels carrying blood away from the heart. [NIH]

**Arterioles:** The smallest divisions of the arteries located between the muscular arteries and the capillaries. [NIH]

**Arteriovenous:** Both arterial and venous; pertaining to or affecting an artery and a vein. [EU]

**Arteritis:** Inflammation of an artery. [NIH]

**Artery:** Vessel-carrying blood from the heart to various parts of the body. [NIH]

**Arthropathy:** Any joint disease. [EU]

**Articular:** Of or pertaining to a joint. [EU]

**Aseptic:** Free from infection or septic material; sterile. [EU]

**Aspartate:** A synthetic amino acid. [NIH]

**Asphyxia:** A pathological condition caused by lack of oxygen, manifested in impending or actual cessation of life. [NIH]

**Aspiration:** The act of inhaling. [NIH]

**Assay:** Determination of the amount of a particular constituent of a mixture, or of the biological or pharmacological potency of a drug. [EU]

**Astringents:** Agents, usually topical, that cause the contraction of tissues for the control of bleeding or secretions. [NIH]

**Astrocytes:** The largest and most numerous neuroglial cells in the brain and spinal cord. Astrocytes (from "star" cells) are irregularly shaped with many long processes, including those with "end feet" which form the glial (limiting) membrane and directly and indirectly contribute to the blood brain barrier. They regulate the extracellular ionic and chemical environment, and "reactive astrocytes" (along with microglia) respond to injury. Astrocytes have high- affinity transmitter uptake systems, voltage-dependent and transmitter-gated ion channels, and can release transmitter, but their role in signaling (as in many other functions) is not well understood. [NIH]

**Asymptomatic:** Having no signs or symptoms of disease. [NIH]

**Ataxia:** Impairment of the ability to perform smoothly coordinated voluntary movements. This condition may affect the limbs, trunk, eyes, pharnyx, larnyx, and other structures. Ataxia may result from impaired sensory or motor function. Sensory ataxia may result from posterior column injury or peripheral nerve diseases. Motor ataxia may be associated with cerebellar diseases; cerebral cortex diseases; thalamic diseases; basal ganglia diseases; injury to the red nucleus; and other conditions. [NIH]

**Atmospheric Pressure:** The pressure at any point in an atmosphere due solely to the weight of the atmospheric gases above the point concerned. [NIH]

**Atopic:** Pertaining to an atopen or to atopy; allergic. [EU]

**Atrial:** Pertaining to an atrium. [EU]

**Atrium:** A chamber; used in anatomical nomenclature to designate a chamber affording entrance to another structure or organ. Usually used alone to designate an atrium of the heart. [EU]

**Atrophy:** Decrease in the size of a cell, tissue, organ, or multiple organs, associated with a variety of pathological conditions such as abnormal cellular changes, ischemia, malnutrition, or hormonal changes. [NIH]

**Atypical:** Irregular; not conformable to the type; in microbiology, applied specifically to strains of unusual type. [EU]

**Auditory:** Pertaining to the sense of hearing. [EU]

**Auditory nerve:** The eight cranial nerve; also called vestibulocochlear nerve or acoustic nerve. [NIH]

**Autoantibodies:** Antibodies that react with self-antigens (autoantigens) of the organism that produced them. [NIH]

**Autoantigens:** Endogenous tissue constituents that have the ability to interact with autoantibodies and cause an immune response. [NIH]

**Autoimmune disease:** A condition in which the body recognizes its own tissues as foreign and directs an immune response against them. [NIH]

**Autoimmune Hepatitis:** A liver disease caused when the body's immune system destroys liver cells for no known reason. [NIH]

**Autoimmunity:** Process whereby the immune system reacts against the body's own tissues. Autoimmunity may produce or be caused by autoimmune diseases. [NIH]

**Autologous:** Taken from an individual's own tissues, cells, or DNA. [NIH]

**Autologous bone marrow transplantation:** A procedure in which bone marrow is removed from a person, stored, and then given back to the person after intensive treatment. [NIH]

**Autonomic:** Self-controlling; functionally independent. [EU]

**Autonomic Nervous System:** The enteric, parasympathetic, and sympathetic nervous systems taken together. Generally speaking, the autonomic nervous system regulates the internal environment during both peaceful activity and physical or emotional stress. Autonomic activity is controlled and integrated by the central nervous system, especially the hypothalamus and the solitary nucleus, which receive information relayed from visceral afferents; these and related central and sensory structures are sometimes (but not here) considered to be part of the autonomic nervous system itself. [NIH]

**Autonomic Neuropathy:** A disease of the nerves affecting mostly the internal organs such as the bladder muscles, the cardiovascular system, the digestive tract, and the genital organs. These nerves are not under a person's conscious control and function automatically. Also called visceral neuropathy. [NIH]

**Autopsy:** Postmortem examination of the body. [NIH]

**Axonal:** Condition associated with metabolic derangement of the entire neuron and is manifest by degeneration of the distal portion of the nerve fiber. [NIH]

**Axons:** Nerve fibers that are capable of rapidly conducting impulses away from the neuron cell body. [NIH]

**Axotomy:** Transection or severing of an axon. This type of denervation is used often in experimental studies on neuronal physiology and neuronal death or survival, toward an understanding of nervous system disease. [NIH]

**Bacteria:** Unicellular prokaryotic microorganisms which generally possess rigid cell walls, multiply by cell division, and exhibit three principal forms: round or coccal, rodlike or bacillary, and spiral or spirochetal. [NIH]

**Bacteriophage:** A virus whose host is a bacterial cell; A virus that exclusively infects bacteria. It generally has a protein coat surrounding the genome (DNA or RNA). One of the coliphages most extensively studied is the lambda phage, which is also one of the most important. [NIH]

**Bacterium:** Microscopic organism which may have a spherical, rod-like, or spiral unicellular or non-cellular body. Bacteria usually reproduce through asexual processes. [NIH]

**Basal Ganglia:** Large subcortical nuclear masses derived from the telencephalon and located in the basal regions of the cerebral hemispheres. [NIH]

**Basal Ganglia Diseases:** Diseases of the basal ganglia including the putamen; globus pallidus; claustrum; amygdala; and caudate nucleus. Dyskinesias (most notably involuntary movements and alterations of the rate of movement) represent the primary clinical manifestations of these disorders. Common etiologies include cerebrovascular disease;

neurodegenerative diseases; and craniocerebral trauma. [NIH]

**Base:** In chemistry, the nonacid part of a salt; a substance that combines with acids to form salts; a substance that dissociates to give hydroxide ions in aqueous solutions; a substance whose molecule or ion can combine with a proton (hydrogen ion); a substance capable of donating a pair of electrons (to an acid) for the formation of a coordinate covalent bond. [EU]

**Basement Membrane:** Ubiquitous supportive tissue adjacent to epithelium and around smooth and striated muscle cells. This tissue contains intrinsic macromolecular components such as collagen, laminin, and sulfated proteoglycans. As seen by light microscopy one of its subdivisions is the basal (basement) lamina. [NIH]

**Basophils:** Granular leukocytes characterized by a relatively pale-staining, lobate nucleus and cytoplasm containing coarse dark-staining granules of variable size and stainable by basic dyes. [NIH]

**Benign:** Not cancerous; does not invade nearby tissue or spread to other parts of the body. [NIH]

**Beta-pleated:** Particular three-dimensional pattern of amyloidoses. [NIH]

**Bilateral:** Affecting both the right and left side of body. [NIH]

**Bile:** An emulsifying agent produced in the liver and secreted into the duodenum. Its composition includes bile acids and salts, cholesterol, and electrolytes. It aids digestion of fats in the duodenum. [NIH]

**Bile Acids:** Acids made by the liver that work with bile to break down fats. [NIH]

**Biliary:** Having to do with the liver, bile ducts, and/or gallbladder. [NIH]

**Bioavailability:** The degree to which a drug or other substance becomes available to the target tissue after administration. [EU]

**Biochemical:** Relating to biochemistry; characterized by, produced by, or involving chemical reactions in living organisms. [EU]

**Biological response modifier:** BRM. A substance that stimulates the body's response to infection and disease. [NIH]

**Biological therapy:** Treatment to stimulate or restore the ability of the immune system to fight infection and disease. Also used to lessen side effects that may be caused by some cancer treatments. Also known as immunotherapy, biotherapy, or biological response modifier (BRM) therapy. [NIH]

**Biomolecular:** A scientific field at the interface between advanced computing and biotechnology. [NIH]

**Biopsy:** Removal and pathologic examination of specimens in the form of small pieces of tissue from the living body. [NIH]

**Biopsy specimen:** Tissue removed from the body and examined under a microscope to determine whether disease is present. [NIH]

**Biotechnology:** Body of knowledge related to the use of organisms, cells or cell-derived constituents for the purpose of developing products which are technically, scientifically and clinically useful. Alteration of biologic function at the molecular level (i.e., genetic engineering) is a central focus; laboratory methods used include transfection and cloning technologies, sequence and structure analysis algorithms, computer databases, and gene and protein structure function analysis and prediction. [NIH]

**Biotin:** Hexahydro-2-oxo-1H-thieno(3,4-d)imidazole-4-pentanoic acid. Growth factor present in minute amounts in every living cell. It occurs mainly bound to proteins or polypeptides and is abundant in liver, kidney, pancreas, yeast, and milk.The biotin content

of cancerous tissue is higher than that of normal tissue. [NIH]

**Bladder:** The organ that stores urine. [NIH]

**Bloating:** Fullness or swelling in the abdomen that often occurs after meals. [NIH]

**Blood Cell Count:** A count of the number of leukocytes and erythrocytes per unit volume in a sample of venous blood. A complete blood count (CBC) also includes measurement of the hemoglobin, hematocrit, and erythrocyte indices. [NIH]

**Blood Coagulation:** The process of the interaction of blood coagulation factors that results in an insoluble fibrin clot. [NIH]

**Blood Glucose:** Glucose in blood. [NIH]

**Blood Platelets:** Non-nucleated disk-shaped cells formed in the megakaryocyte and found in the blood of all mammals. They are mainly involved in blood coagulation. [NIH]

**Blood pressure:** The pressure of blood against the walls of a blood vessel or heart chamber. Unless there is reference to another location, such as the pulmonary artery or one of the heart chambers, it refers to the pressure in the systemic arteries, as measured, for example, in the forearm. [NIH]

**Blood vessel:** A tube in the body through which blood circulates. Blood vessels include a network of arteries, arterioles, capillaries, venules, and veins. [NIH]

**Blood Volume:** Volume of circulating blood. It is the sum of the plasma volume and erythrocyte volume. [NIH]

**Blood-Brain Barrier:** Specialized non-fenestrated tightly-joined endothelial cells (tight junctions) that form a transport barrier for certain substances between the cerebral capillaries and the brain tissue. [NIH]

**Body Composition:** The relative amounts of various components in the body, such as percent body fat. [NIH]

**Body Fluids:** Liquid components of living organisms. [NIH]

**Body Mass Index:** One of the anthropometric measures of body mass; it has the highest correlation with skinfold thickness or body density. [NIH]

**Body Regions:** Anatomical areas of the body. [NIH]

**Bolus:** A single dose of drug usually injected into a blood vessel over a short period of time. Also called bolus infusion. [NIH]

**Bolus infusion:** A single dose of drug usually injected into a blood vessel over a short period of time. Also called bolus. [NIH]

**Bone Density:** The amount of mineral per square centimeter of bone. This is the definition used in clinical practice. Actual bone density would be expressed in grams per milliliter. It is most frequently measured by photon absorptiometry or x-ray computed tomography. [NIH]

**Bone Marrow:** The soft tissue filling the cavities of bones. Bone marrow exists in two types, yellow and red. Yellow marrow is found in the large cavities of large bones and consists mostly of fat cells and a few primitive blood cells. Red marrow is a hematopoietic tissue and is the site of production of erythrocytes and granular leukocytes. Bone marrow is made up of a framework of connective tissue containing branching fibers with the frame being filled with marrow cells. [NIH]

**Bone Marrow Transplantation:** The transference of bone marrow from one human or animal to another. [NIH]

**Bowel:** The long tube-shaped organ in the abdomen that completes the process of digestion. There is both a small and a large bowel. Also called the intestine. [NIH]

**Bowel Movement:** Body wastes passed through the rectum and anus. [NIH]

**Brachial:** All the nerves from the arm are ripped from the spinal cord. [NIH]

**Brachial Plexus:** The large network of nerve fibers which distributes the innervation of the upper extremity. The brachial plexus extends from the neck into the axilla. In humans, the nerves of the plexus usually originate from the lower cervical and the first thoracic spinal cord segments (C5-C8 and T1), but variations are not uncommon. [NIH]

**Bradykinesia:** Abnormal slowness of movement; sluggishness of physical and mental responses. [EU]

**Brain Diseases:** Pathologic conditions affecting the brain, which is composed of the intracranial components of the central nervous system. This includes (but is not limited to) the cerebral cortex; intracranial white matter; basal ganglia; thalamus; hypothalamus; brain stem; and cerebellum. [NIH]

**Brain Stem:** The part of the brain that connects the cerebral hemispheres with the spinal cord. It consists of the mesencephalon, pons, and medulla oblongata. [NIH]

**Branch:** Most commonly used for branches of nerves, but applied also to other structures. [NIH]

**Breakdown:** A physical, metal, or nervous collapse. [NIH]

**Bronchial:** Pertaining to one or more bronchi. [EU]

**Buccal:** Pertaining to or directed toward the cheek. In dental anatomy, used to refer to the buccal surface of a tooth. [EU]

**Cachexia:** General ill health, malnutrition, and weight loss, usually associated with chronic disease. [NIH]

**Calcitonin:** A peptide hormone that lowers calcium concentration in the blood. In humans, it is released by thyroid cells and acts to decrease the formation and absorptive activity of osteoclasts. Its role in regulating plasma calcium is much greater in children and in certain diseases than in normal adults. [NIH]

**Calcium:** A basic element found in nearly all organized tissues. It is a member of the alkaline earth family of metals with the atomic symbol Ca, atomic number 20, and atomic weight 40. Calcium is the most abundant mineral in the body and combines with phosphorus to form calcium phosphate in the bones and teeth. It is essential for the normal functioning of nerves and muscles and plays a role in blood coagulation (as factor IV) and in many enzymatic processes. [NIH]

**Calculi:** An abnormal concretion occurring mostly in the urinary and biliary tracts, usually composed of mineral salts. Also called stones. [NIH]

**Caloric intake:** Refers to the number of calories (energy content) consumed. [NIH]

**Calpain:** Cysteine proteinase found in many tissues. Hydrolyzes a variety of endogenous proteins including neuropeptides, cytoskeletal proteins, proteins from smooth muscle, cardiac muscle, liver, platelets and erythrocytes. Two subclasses having high and low calcium sensitivity are known. Removes Z-discs and M-lines from myofibrils. Activates phosphorylase kinase and cyclic nucleotide-independent protein kinase. [NIH]

**Cannabidiol:** Compound isolated from Cannabis sativa extract. [NIH]

**Cannabinoids:** Compounds extracted from Cannabis sativa L. and metabolites having the cannabinoid structure. The most active constituents are tetrahydrocannabinol, cannabinol, and cannabidiol. [NIH]

**Cannabinol:** A physiologically inactive constituent of Cannabis sativa L. [NIH]

**Capillary:** Any one of the minute vessels that connect the arterioles and venules, forming a

network in nearly all parts of the body. Their walls act as semipermeable membranes for the interchange of various substances, including fluids, between the blood and tissue fluid; called also vas capillare. [EU]

**Capillary Permeability:** Property of blood capillary walls that allows for the selective exchange of substances. Small lipid-soluble molecules such as carbon dioxide and oxygen move freely by diffusion. Water and water-soluble molecules cannot pass through the endothelial walls and are dependent on microscopic pores. These pores show narrow areas (tight junctions) which may limit large molecule movement. [NIH]

**Capsaicin:** Cytotoxic alkaloid from various species of Capsicum (pepper, paprika), of the Solanaceae. [NIH]

**Capsicum:** A genus of Solanaceous shrubs that yield capsaicin. Several varieties have sweet or pungent edible fruits that are used as vegetables when fresh and spices when the pods are dried. [NIH]

**Capsules:** Hard or soft soluble containers used for the oral administration of medicine. [NIH]

**Carbamazepine:** An anticonvulsant used to control grand mal and psychomotor or focal seizures. Its mode of action is not fully understood, but some of its actions resemble those of phenytoin; although there is little chemical resemblance between the two compounds, their three-dimensional structure is similar. [NIH]

**Carbohydrate:** An aldehyde or ketone derivative of a polyhydric alcohol, particularly of the pentahydric and hexahydric alcohols. They are so named because the hydrogen and oxygen are usually in the proportion to form water, (CH2O)n. The most important carbohydrates are the starches, sugars, celluloses, and gums. They are classified into mono-, di-, tri-, poly- and heterosaccharides. [EU]

**Carbon Dioxide:** A colorless, odorless gas that can be formed by the body and is necessary for the respiration cycle of plants and animals. [NIH]

**Carboplatin:** An organoplatinum compound that possesses antineoplastic activity. [NIH]

**Carboxy:** Cannabinoid. [NIH]

**Carboxy-terminal:** The end of any polypeptide or protein that bears a free carboxyl group. [NIH]

**Carcinogen:** Any substance that causes cancer. [NIH]

**Carcinogenic:** Producing carcinoma. [EU]

**Carcinoma:** Cancer that begins in the skin or in tissues that line or cover internal organs. [NIH]

**Cardiac:** Having to do with the heart. [NIH]

**Cardiomyopathy:** A general diagnostic term designating primary myocardial disease, often of obscure or unknown etiology. [EU]

**Cardiotoxicity:** Toxicity that affects the heart. [NIH]

**Cardiovascular:** Having to do with the heart and blood vessels. [NIH]

**Cardiovascular System:** The heart and the blood vessels by which blood is pumped and circulated through the body. [NIH]

**Carnitine:** Constituent of striated muscle and liver. It is used therapeutically to stimulate gastric and pancreatic secretions and in the treatment of hyperlipoproteinemias. [NIH]

**Carotene:** The general name for a group of pigments found in green, yellow, and leafy vegetables, and yellow fruits. The pigments are fat-soluble, unsaturated aliphatic hydrocarbons functioning as provitamins and are converted to vitamin A through enzymatic processes in the intestinal wall. [NIH]

**Carpal Tunnel Syndrome:** A median nerve injury inside the carpal tunnel that results in symptoms of pain, numbness, tingling, clumsiness, and a lack of sweating, which can be caused by work with certain hand and wrist postures. [NIH]

**Case report:** A detailed report of the diagnosis, treatment, and follow-up of an individual patient. Case reports also contain some demographic information about the patient (for example, age, gender, ethnic origin). [NIH]

**Case series:** A group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment. [NIH]

**Cataracts:** In medicine, an opacity of the crystalline lens of the eye obstructing partially or totally its transmission of light. [NIH]

**Catecholamine:** A group of chemical substances manufactured by the adrenal medulla and secreted during physiological stress. [NIH]

**Cathode:** An electrode, usually an incandescent filament of tungsten, which emits electrons in an X-ray tube. [NIH]

**Cations:** Postively charged atoms, radicals or groups of atoms which travel to the cathode or negative pole during electrolysis. [NIH]

**Causal:** Pertaining to a cause; directed against a cause. [EU]

**Cause of Death:** Factors which produce cessation of all vital bodily functions. They can be analyzed from an epidemiologic viewpoint. [NIH]

**Cell:** The individual unit that makes up all of the tissues of the body. All living things are made up of one or more cells. [NIH]

**Cell Count:** A count of the number of cells of a specific kind, usually measured per unit volume of sample. [NIH]

**Cell Death:** The termination of the cell's ability to carry out vital functions such as metabolism, growth, reproduction, responsiveness, and adaptability. [NIH]

**Cell Differentiation:** Progressive restriction of the developmental potential and increasing specialization of function which takes place during the development of the embryo and leads to the formation of specialized cells, tissues, and organs. [NIH]

**Cell Division:** The fission of a cell. [NIH]

**Cell membrane:** Cell membrane = plasma membrane. The structure enveloping a cell, enclosing the cytoplasm, and forming a selective permeability barrier; it consists of lipids, proteins, and some carbohydrates, the lipids thought to form a bilayer in which integral proteins are embedded to varying degrees. [EU]

**Cell proliferation:** An increase in the number of cells as a result of cell growth and cell division. [NIH]

**Cell Respiration:** The metabolic process of all living cells (animal and plant) in which oxygen is used to provide a source of energy for the cell. [NIH]

**Cell Size:** The physical dimensions of a cell. It refers mainly to changes in dimensions correlated with physiological or pathological changes in cells. [NIH]

**Cell Survival:** The span of viability of a cell characterized by the capacity to perform certain functions such as metabolism, growth, reproduction, some form of responsiveness, and adaptability. [NIH]

**Cell Transplantation:** Transference of cells within an individual, between individuals of the

same species, or between individuals of different species. [NIH]

**Cellulitis:** An acute, diffuse, and suppurative inflammation of loose connective tissue, particularly the deep subcutaneous tissues, and sometimes muscle, which is most commonly seen as a result of infection of a wound, ulcer, or other skin lesions. [NIH]

**Central Nervous System:** The main information-processing organs of the nervous system, consisting of the brain, spinal cord, and meninges. [NIH]

**Central Nervous System Infections:** Pathogenic infections of the brain, spinal cord, and meninges. DNA virus infections; RNA virus infections; bacterial infections; mycoplasma infections; Spirochaetales infections; fungal infections; protozoan infections; helminthiasis; and prion diseases may involve the central nervous system as a primary or secondary process. [NIH]

**Cerebellar:** Pertaining to the cerebellum. [EU]

**Cerebellar Diseases:** Diseases that affect the structure or function of the cerebellum. Cardinal manifestations of cerebellar dysfunction include dysmetria, gait ataxia, and muscle hypotonia. [NIH]

**Cerebellum:** Part of the metencephalon that lies in the posterior cranial fossa behind the brain stem. It is concerned with the coordination of movement. [NIH]

**Cerebral:** Of or pertaining of the cerebrum or the brain. [EU]

**Cerebral Cortex:** The thin layer of gray matter on the surface of the cerebral hemisphere that develops from the telencephalon and folds into gyri. It reaches its highest development in man and is responsible for intellectual faculties and higher mental functions. [NIH]

**Cerebral Palsy:** Refers to a motor disability caused by a brain dysfunction. [NIH]

**Cerebrospinal:** Pertaining to the brain and spinal cord. [EU]

**Cerebrospinal fluid:** CSF. The fluid flowing around the brain and spinal cord. Cerebrospinal fluid is produced in the ventricles in the brain. [NIH]

**Cerebrovascular:** Pertaining to the blood vessels of the cerebrum, or brain. [EU]

**Cerebrum:** The largest part of the brain. It is divided into two hemispheres, or halves, called the cerebral hemispheres. The cerebrum controls muscle functions of the body and also controls speech, emotions, reading, writing, and learning. [NIH]

**Cervical:** Relating to the neck, or to the neck of any organ or structure. Cervical lymph nodes are located in the neck; cervical cancer refers to cancer of the uterine cervix, which is the lower, narrow end (the "neck") of the uterus. [NIH]

**Character:** In current usage, approximately equivalent to personality. The sum of the relatively fixed personality traits and habitual modes of response of an individual. [NIH]

**Chelation:** Combination with a metal in complexes in which the metal is part of a ring. [EU]

**Chemotactic Factors:** Chemical substances that attract or repel cells or organisms. The concept denotes especially those factors released as a result of tissue injury, invasion, or immunologic activity, that attract leukocytes, macrophages, or other cells to the site of infection or insult. [NIH]

**Chemotherapeutic agent:** A drug used to treat cancer. [NIH]

**Chemotherapeutics:** Noun plural but singular or plural in constructions : chemotherapy. [EU]

**Chemotherapy:** Treatment with anticancer drugs. [NIH]

**Chest Pain:** Pressure, burning, or numbness in the chest. [NIH]

**Chimeras:** Organism that contains a mixture of genetically different cells. [NIH]

**Chin:** The anatomical frontal portion of the mandible, also known as the mentum, that contains the line of fusion of the two separate halves of the mandible (symphysis menti). This line of fusion divides inferiorly to enclose a triangular area called the mental protuberance. On each side, inferior to the second premolar tooth, is the mental foramen for the passage of blood vessels and a nerve. [NIH]

**Chlorambucil:** An anticancer drug that belongs to the family of drugs called alkylating agents. [NIH]

**Cholesterol:** The principal sterol of all higher animals, distributed in body tissues, especially the brain and spinal cord, and in animal fats and oils. [NIH]

**Cholinergic:** Resembling acetylcholine in pharmacological action; stimulated by or releasing acetylcholine or a related compound. [EU]

**Chromatin:** The material of chromosomes. It is a complex of DNA, histones, and nonhistone proteins (chromosomal proteins, non-histone) found within the nucleus of a cell. [NIH]

**Chromic:** Catgut sterilized and impregnated with chromium trioxide. [NIH]

**Chromium:** A trace element that plays a role in glucose metabolism. It has the atomic symbol Cr, atomic number 24, and atomic weight 52. According to the Fourth Annual Report on Carcinogens (NTP85-002,1985), chromium and some of its compounds have been listed as known carcinogens. [NIH]

**Chromosomal:** Pertaining to chromosomes. [EU]

**Chromosome:** Part of a cell that contains genetic information. Except for sperm and eggs, all human cells contain 46 chromosomes. [NIH]

**Chronic:** A disease or condition that persists or progresses over a long period of time. [NIH]

**Chronic Disease:** Disease or ailment of long duration. [NIH]

**Chronic lymphocytic leukemia:** A slowly progressing disease in which too many white blood cells (called lymphocytes) are found in the body. [NIH]

**Chronic renal:** Slow and progressive loss of kidney function over several years, often resulting in end-stage renal disease. People with end-stage renal disease need dialysis or transplantation to replace the work of the kidneys. [NIH]

**Chylomicrons:** A class of lipoproteins that carry dietary cholesterol and triglycerides from the small intestines to the tissues. [NIH]

**CIS:** Cancer Information Service. The CIS is the National Cancer Institute's link to the public, interpreting and explaining research findings in a clear and understandable manner, and providing personalized responses to specific questions about cancer. Access the CIS by calling 1-800-4-CANCER, or by using the Web site at http://cis.nci.nih.gov. [NIH]

**Cisplatin:** An inorganic and water-soluble platinum complex. After undergoing hydrolysis, it reacts with DNA to produce both intra and interstrand crosslinks. These crosslinks appear to impair replication and transcription of DNA. The cytotoxicity of cisplatin correlates with cellular arrest in the G2 phase of the cell cycle. [NIH]

**Clamp:** A u-shaped steel rod used with a pin or wire for skeletal traction in the treatment of certain fractures. [NIH]

**Claudication:** Limping or lameness. [EU]

**Clavicle:** A long bone of the shoulder girdle. [NIH]

**Clinical Medicine:** The study and practice of medicine by direct examination of the patient. [NIH]

**Clinical study:** A research study in which patients receive treatment in a clinic or other

medical facility. Reports of clinical studies can contain results for single patients (case reports) or many patients (case series or clinical trials). [NIH]

**Clinical trial:** A research study that tests how well new medical treatments or other interventions work in people. Each study is designed to test new methods of screening, prevention, diagnosis, or treatment of a disease. [NIH]

**Clone:** The term "clone" has acquired a new meaning. It is applied specifically to the bits of inserted foreign DNA in the hybrid molecules of the population. Each inserted segment originally resided in the DNA of a complex genome amid millions of other DNA segment. [NIH]

**Cloning:** The production of a number of genetically identical individuals; in genetic engineering, a process for the efficient replication of a great number of identical DNA molecules. [NIH]

**Cochlea:** The part of the internal ear that is concerned with hearing. It forms the anterior part of the labyrinth, is conical, and is placed almost horizontally anterior to the vestibule. [NIH]

**Cochlear:** Of or pertaining to the cochlea. [EU]

**Cochlear Implants:** Electronic devices implanted beneath the skin with electrodes to the cochlear nerve to create sound sensation in persons with sensorineural deafness. [NIH]

**Cochlear Nerve:** The cochlear part of the 8th cranial nerve (vestibulocochlear nerve). The cochlear nerve fibers originate from neurons of the spiral ganglion and project peripherally to cochlear hair cells and centrally to the cochlear nuclei (cochlear nucleus) of the brain stem. They mediate the sense of hearing. [NIH]

**Codon:** A set of three nucleotides in a protein coding sequence that specifies individual amino acids or a termination signal (codon, terminator). Most codons are universal, but some organisms do not produce the transfer RNAs (RNA, transfer) complementary to all codons. These codons are referred to as unassigned codons (codons, nonsense). [NIH]

**Coenzyme:** An organic nonprotein molecule, frequently a phosphorylated derivative of a water-soluble vitamin, that binds with the protein molecule (apoenzyme) to form the active enzyme (holoenzyme). [EU]

**Cofactor:** A substance, microorganism or environmental factor that activates or enhances the action of another entity such as a disease-causing agent. [NIH]

**Cohort Studies:** Studies in which subsets of a defined population are identified. These groups may or may not be exposed to factors hypothesized to influence the probability of the occurrence of a particular disease or other outcome. Cohorts are defined populations which, as a whole, are followed in an attempt to determine distinguishing subgroup characteristics. [NIH]

**Colitis:** Inflammation of the colon. [NIH]

**Collagen:** A polypeptide substance comprising about one third of the total protein in mammalian organisms. It is the main constituent of skin, connective tissue, and the organic substance of bones and teeth. Different forms of collagen are produced in the body but all consist of three alpha-polypeptide chains arranged in a triple helix. Collagen is differentiated from other fibrous proteins, such as elastin, by the content of proline, hydroxyproline, and hydroxylysine; by the absence of tryptophan; and particularly by the high content of polar groups which are responsible for its swelling properties. [NIH]

**Collagen disease:** A term previously used to describe chronic diseases of the connective tissue (e.g., rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis), but now is thought to be more appropriate for diseases associated with defects in collagen, which is a component of the connective tissue. [NIH]

**Collapse:** 1. A state of extreme prostration and depression, with failure of circulation. 2. Abnormal falling in of the walls of any part of organ. [EU]

**Colon:** The long, coiled, tubelike organ that removes water from digested food. The remaining material, solid waste called stool, moves through the colon to the rectum and leaves the body through the anus. [NIH]

**Complement:** A term originally used to refer to the heat-labile factor in serum that causes immune cytolysis, the lysis of antibody-coated cells, and now referring to the entire functionally related system comprising at least 20 distinct serum proteins that is the effector not only of immune cytolysis but also of other biologic functions. Complement activation occurs by two different sequences, the classic and alternative pathways. The proteins of the classic pathway are termed 'components of complement' and are designated by the symbols C1 through C9. C1 is a calcium-dependent complex of three distinct proteins C1q, C1r and C1s. The proteins of the alternative pathway (collectively referred to as the properdin system) and complement regulatory proteins are known by semisystematic or trivial names. Fragments resulting from proteolytic cleavage of complement proteins are designated with lower-case letter suffixes, e.g., C3a. Inactivated fragments may be designated with the suffix 'i', e.g. C3bi. Activated components or complexes with biological activity are designated by a bar over the symbol e.g. C1 or C4b,2a. The classic pathway is activated by the binding of C1 to classic pathway activators, primarily antigen-antibody complexes containing IgM, IgG1, IgG3; C1q binds to a single IgM molecule or two adjacent IgG molecules. The alternative pathway can be activated by IgA immune complexes and also by nonimmunologic materials including bacterial endotoxins, microbial polysaccharides, and cell walls. Activation of the classic pathway triggers an enzymatic cascade involving C1, C4, C2 and C3; activation of the alternative pathway triggers a cascade involving C3 and factors B, D and P. Both result in the cleavage of C5 and the formation of the membrane attack complex. Complement activation also results in the formation of many biologically active complement fragments that act as anaphylatoxins, opsonins, or chemotactic factors. [EU]

**Complementary and alternative medicine:** CAM. Forms of treatment that are used in addition to (complementary) or instead of (alternative) standard treatments. These practices are not considered standard medical approaches. CAM includes dietary supplements, megadose vitamins, herbal preparations, special teas, massage therapy, magnet therapy, spiritual healing, and meditation. [NIH]

**Complementary medicine:** Practices not generally recognized by the medical community as standard or conventional medical approaches and used to enhance or complement the standard treatments. Complementary medicine includes the taking of dietary supplements, megadose vitamins, and herbal preparations; the drinking of special teas; and practices such as massage therapy, magnet therapy, spiritual healing, and meditation. [NIH]

**Compliance:** Distensibility measure of a chamber such as the lungs (lung compliance) or bladder. Compliance is expressed as a change in volume per unit change in pressure. [NIH]

**Compulsions:** In psychology, an irresistible urge, sometimes amounting to obsession to perform a particular act which usually is carried out against the performer's will or better judgment. [NIH]

**Computational Biology:** A field of biology concerned with the development of techniques for the collection and manipulation of biological data, and the use of such data to make biological discoveries or predictions. This field encompasses all computational methods and theories applicable to molecular biology and areas of computer-based techniques for solving biological problems including manipulation of models and datasets. [NIH]

**Concentric:** Having a common center of curvature or symmetry. [NIH]

**Concomitant:** Accompanying; accessory; joined with another. [EU]

**Conduction:** The transfer of sound waves, heat, nervous impulses, or electricity. [EU]

**Cones:** One type of specialized light-sensitive cells (photoreceptors) in the retina that provide sharp central vision and color vision. [NIH]

**Conjugated:** Acting or operating as if joined; simultaneous. [EU]

**Conjugation:** 1. The act of joining together or the state of being conjugated. 2. A sexual process seen in bacteria, ciliate protozoa, and certain fungi in which nuclear material is exchanged during the temporary fusion of two cells (conjugants). In bacterial genetics a form of sexual reproduction in which a donor bacterium (male) contributes some, or all, of its DNA (in the form of a replicated set) to a recipient (female) which then incorporates differing genetic information into its own chromosome by recombination and passes the recombined set on to its progeny by replication. In ciliate protozoa, two conjugants of separate mating types exchange micronuclear material and then separate, each now being a fertilized cell. In certain fungi, the process involves fusion of two gametes, resulting in union of their nuclei and formation of a zygote. 3. In chemistry, the joining together of two compounds to produce another compound, such as the combination of a toxic product with some substance in the body to form a detoxified product, which is then eliminated. [EU]

**Connective Tissue:** Tissue that supports and binds other tissues. It consists of connective tissue cells embedded in a large amount of extracellular matrix. [NIH]

**Connective Tissue:** Tissue that supports and binds other tissues. It consists of connective tissue cells embedded in a large amount of extracellular matrix. [NIH]

**Connective Tissue Cells:** A group of cells that includes fibroblasts, cartilage cells, adipocytes, smooth muscle cells, and bone cells. [NIH]

**Connective Tissue Diseases:** A heterogeneous group of disorders, some hereditary, others acquired, characterized by abnormal structure or function of one or more of the elements of connective tissue, i.e., collagen, elastin, or the mucopolysaccharides. [NIH]

**Connexins:** A group of homologous proteins which form the intermembrane channels of gap junctions. The connexins are the products of an identified gene family which has both highly conserved and highly divergent regions. The variety contributes to the wide range of functional properties of gap junctions. [NIH]

**Consciousness:** Sense of awareness of self and of the environment. [NIH]

**Constipation:** Infrequent or difficult evacuation of feces. [NIH]

**Constitutional:** 1. Affecting the whole constitution of the body; not local. 2. Pertaining to the constitution. [EU]

**Constriction:** The act of constricting. [NIH]

**Constriction, Pathologic:** The condition of an anatomical structure's being constricted beyond normal dimensions. [NIH]

**Consumption:** Pulmonary tuberculosis. [NIH]

**Contamination:** The soiling or pollution by inferior material, as by the introduction of organisms into a wound, or sewage into a stream. [EU]

**Contracture:** A condition of fixed high resistance to passive stretch of a muscle, resulting from fibrosis of the tissues supporting the muscles or the joints, or from disorders of the muscle fibres. [EU]

**Contraindications:** Any factor or sign that it is unwise to pursue a certain kind of action or treatment, e. g. giving a general anesthetic to a person with pneumonia. [NIH]

**Contralateral:** Having to do with the opposite side of the body. [NIH]

**Contrast Sensitivity:** The ability to detect sharp boundaries (stimuli) and to detect slight

changes in luminance at regions without distinct contours. Psychophysical measurements of this visual function are used to evaluate visual acuity and to detect eye disease. [NIH]

**Controlled clinical trial:** A clinical study that includes a comparison (control) group. The comparison group receives a placebo, another treatment, or no treatment at all. [NIH]

**Convulsions:** A general term referring to sudden and often violent motor activity of cerebral or brainstem origin. Convulsions may also occur in the absence of an electrical cerebral discharge (e.g., in response to hypotension). [NIH]

**Convulsive:** Relating or referring to spasm; affected with spasm; characterized by a spasm or spasms. [NIH]

**Coordination:** Muscular or motor regulation or the harmonious cooperation of muscles or groups of muscles, in a complex action or series of actions. [NIH]

**Cor:** The muscular organ that maintains the circulation of the blood. c. adiposum a heart that has undergone fatty degeneration or that has an accumulation of fat around it; called also fat or fatty, heart. c. arteriosum the left side of the heart, so called because it contains oxygenated (arterial) blood. c. biloculare a congenital anomaly characterized by failure of formation of the atrial and ventricular septums, the heart having only two chambers, a single atrium and a single ventricle, and a common atrioventricular valve. c. bovinum (L. 'ox heart') a greatly enlarged heart due to a hypertrophied left ventricle; called also c. taurinum and bucardia. c. dextrum (L. 'right heart') the right atrium and ventricle. c. hirsutum, c. villosum. c. mobile (obs.) an abnormally movable heart. c. pendulum a heart so movable that it seems to be hanging by the great blood vessels. c. pseudotriloculare biatriatum a congenital cardiac anomaly in which the heart functions as a three-chambered heart because of tricuspid atresia, the right ventricle being extremely small or rudimentary and the right atrium greatly dilated. Blood passes from the right to the left atrium and thence disease due to pulmonary hypertension secondary to disease of the lung, or its blood vessels, with hypertrophy of the right ventricle. [EU]

**Coronary:** Encircling in the manner of a crown; a term applied to vessels; nerves, ligaments, etc. The term usually denotes the arteries that supply the heart muscle and, by extension, a pathologic involvement of them. [EU]

**Coronary Thrombosis:** Presence of a thrombus in a coronary artery, often causing a myocardial infarction. [NIH]

**Corpus:** The body of the uterus. [NIH]

**Corpus Callosum:** Broad plate of dense myelinated fibers that reciprocally interconnect regions of the cortex in all lobes with corresponding regions of the opposite hemisphere. The corpus callosum is located deep in the longitudinal fissure. [NIH]

**Cortex:** The outer layer of an organ or other body structure, as distinguished from the internal substance. [EU]

**Cortical:** Pertaining to or of the nature of a cortex or bark. [EU]

**Cortices:** The outer layer of an organ; used especially of the cerebrum and cerebellum. [NIH]

**Corticosteroid:** Any of the steroids elaborated by the adrenal cortex (excluding the sex hormones of adrenal origin) in response to the release of corticotrophin (adrenocorticotropic hormone) by the pituitary gland, to any of the synthetic equivalents of these steroids, or to angiotensin II. They are divided, according to their predominant biological activity, into three major groups: glucocorticoids, chiefly influencing carbohydrate, fat, and protein metabolism; mineralocorticoids, affecting the regulation of electrolyte and water balance; and C19 androgens. Some corticosteroids exhibit both types of activity in varying degrees, and others exert only one type of effect. The corticosteroids are used clinically for hormonal

replacement therapy, for suppression of ACTH secretion by the anterior pituitary, as antineoplastic, antiallergic, and anti-inflammatory agents, and to suppress the immune response. Called also adrenocortical hormone and corticoid. [EU]

**Coxsackievirus Infections:** A heterogeneous group of infections produced by coxsackieviruses, including herpangina, aseptic meningitis, a common-cold-like syndrome, a non-paralytic poliomyelitis-like syndrome, epidemic pleurodynia, and a serious myocarditis. [NIH]

**Coxsackieviruses:** A heterogeneous group of the genus enterovirus found in association with various diseases in man and other animals. Two groups (A and B) have been identified with a number of serotypes in each. The name is derived from a village in New York State where the virus was first identified. [NIH]

**Cranial:** Pertaining to the cranium, or to the anterior (in animals) or superior (in humans) end of the body. [EU]

**Craniocerebral Trauma:** Traumatic injuries involving the cranium and intracranial structures (i.e., brain; cranial nerves; meninges; and other structures). Injuries may be classified by whether or not the skull is penetrated (i.e., penetrating vs. nonpenetrating) or whether there is an associated hemorrhage. [NIH]

**Creatine:** An amino acid that occurs in vertebrate tissues and in urine. In muscle tissue, creatine generally occurs as phosphocreatine. Creatine is excreted as creatinine in the urine. [NIH]

**Creatine Kinase:** A transferase that catalyzes formation of phosphocreatine from ATP + creatine. The reaction stores ATP energy as phosphocreatine. Three cytoplasmic isoenzymes have been identified in human tissues: MM from skeletal muscle, MB from myocardial tissue, and BB from nervous tissue as well as a mitochondrial isoenzyme. Macro-creatine kinase refers to creatine kinase complexed with other serum proteins. EC 2.7.3.2. [NIH]

**Creatinine:** A compound that is excreted from the body in urine. Creatinine levels are measured to monitor kidney function. [NIH]

**Crossing-over:** The exchange of corresponding segments between chromatids of homologous chromosomes during meiosia, forming a chiasma. [NIH]

**Cross-Sectional Studies:** Studies in which the presence or absence of disease or other health-related variables are determined in each member of the study population or in a representative sample at one particular time. This contrasts with longitudinal studies which are followed over a period of time. [NIH]

**Cryoglobulinemia:** A condition characterized by the presence of abnormal or abnormal quantities of cryoglobulins in the blood. They are precipitated into the microvasculature on exposure to cold and cause restricted blood flow in exposed areas. [NIH]

**Cues:** Signals for an action; that specific portion of a perceptual field or pattern of stimuli to which a subject has learned to respond. [NIH]

**Cumulative Trauma Disorders:** Harmful and painful condition caused by overuse or overexertion of some part of the musculoskeletal system, often resulting from work-related physical activities. It is characterized by inflammation, pain, or dysfunction of the involved joints, bones, ligaments, and nerves. [NIH]

**Curative:** Tending to overcome disease and promote recovery. [EU]

**Cutaneous:** Having to do with the skin. [NIH]

**Cyanosis:** A bluish or purplish discoloration of the skin and mucous membranes due to an increase in the amount of deoxygenated hemoglobin in the blood or a structural defect in the hemoglobin molecule. [NIH]

**Cyclic:** Pertaining to or occurring in a cycle or cycles; the term is applied to chemical compounds that contain a ring of atoms in the nucleus. [EU]

**Cyclophosphamide:** Precursor of an alkylating nitrogen mustard antineoplastic and immunosuppressive agent that must be activated in the liver to form the active aldophosphamide. It is used in the treatment of lymphomas, leukemias, etc. Its side effect, alopecia, has been made use of in defleecing sheep. Cyclophosphamide may also cause sterility, birth defects, mutations, and cancer. [NIH]

**Cytarabine:** An anticancer drug that belongs to the family of drugs called antimetabolites. [NIH]

**Cytochrome:** Any electron transfer hemoprotein having a mode of action in which the transfer of a single electron is effected by a reversible valence change of the central iron atom of the heme prosthetic group between the +2 and +3 oxidation states; classified as cytochromes a in which the heme contains a formyl side chain, cytochromes b, which contain protoheme or a closely similar heme that is not covalently bound to the protein, cytochromes c in which protoheme or other heme is covalently bound to the protein, and cytochromes d in which the iron-tetrapyrrole has fewer conjugated double bonds than the hemes have. Well-known cytochromes have been numbered consecutively within groups and are designated by subscripts (beginning with no subscript), e.g. cytochromes c, c1, C2, . New cytochromes are named according to the wavelength in nanometres of the absorption maximum of the a-band of the iron (II) form in pyridine, e.g., c-555. [EU]

**Cytochrome b:** Cytochromes (electron-transporting proteins) with protoheme or a related heme as the prosthetic group. The prosthetic group is not covalently bound to the protein moiety. [NIH]

**Cytochrome-c Oxidase:** An enzyme complex of the inner mitochondrial membrane that catalyzes the reaction between ferrocytochrome c and oxygen to yield ferricytochrome c and water. It is associated with the pumping of protons and the resultant phosphorylation of ADP to ATP. The reaction is the terminal event in the electron transport scheme by which oxygen is used for fuel combustion. EC 1.9.3.1. [NIH]

**Cytokine:** Small but highly potent protein that modulates the activity of many cell types, including T and B cells. [NIH]

**Cytomegalovirus:** A genus of the family Herpesviridae, subfamily Betaherpesvirinae, infecting the salivary glands, liver, spleen, lungs, eyes, and other organs, in which they produce characteristically enlarged cells with intranuclear inclusions. Infection with Cytomegalovirus is also seen as an opportunistic infection in AIDS. [NIH]

**Cytoplasm:** The protoplasm of a cell exclusive of that of the nucleus; it consists of a continuous aqueous solution (cytosol) and the organelles and inclusions suspended in it (phaneroplasm), and is the site of most of the chemical activities of the cell. [EU]

**Cytosine:** A pyrimidine base that is a fundamental unit of nucleic acids. [NIH]

**Cytoskeleton:** The network of filaments, tubules, and interconnecting filamentous bridges which give shape, structure, and organization to the cytoplasm. [NIH]

**Cytotoxic:** Cell-killing. [NIH]

**Cytotoxicity:** Quality of being capable of producing a specific toxic action upon cells of special organs. [NIH]

**Dacarbazine:** An anticancer drug that belongs to the family of drugs called alkylating agents. [NIH]

**Daunorubicin:** Very toxic anthracycline aminoglycoside antibiotic isolated from Streptomyces peucetius and others, used in treatment of leukemias and other neoplasms. [NIH]

**Deamination:** The removal of an amino group (NH2) from a chemical compound. [NIH]

**Decarboxylation:** The removal of a carboxyl group, usually in the form of carbon dioxide, from a chemical compound. [NIH]

**Decompensation:** Failure of compensation; cardiac decompensation is marked by dyspnea, venous engorgement, and edema. [EU]

**Degenerative:** Undergoing degeneration : tending to degenerate; having the character of or involving degeneration; causing or tending to cause degeneration. [EU]

**Deletion:** A genetic rearrangement through loss of segments of DNA (chromosomes), bringing sequences, which are normally separated, into close proximity. [NIH]

**Delusions:** A false belief regarding the self or persons or objects outside the self that persists despite the facts, and is not considered tenable by one's associates. [NIH]

**Dementia:** An acquired organic mental disorder with loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning. The dysfunction is multifaceted and involves memory, behavior, personality, judgment, attention, spatial relations, language, abstract thought, and other executive functions. The intellectual decline is usually progressive, and initially spares the level of consciousness. [NIH]

**Demyelinating Diseases:** Diseases characterized by loss or dysfunction of myelin in the central or peripheral nervous system. [NIH]

**Dendrites:** Extensions of the nerve cell body. They are short and branched and receive stimuli from other neurons. [NIH]

**Density:** The logarithm to the base 10 of the opacity of an exposed and processed film. [NIH]

**Dental Caries:** Localized destruction of the tooth surface initiated by decalcification of the enamel followed by enzymatic lysis of organic structures and leading to cavity formation. If left unchecked, the cavity may penetrate the enamel and dentin and reach the pulp. The three most prominent theories used to explain the etiology of the disase are that acids produced by bacteria lead to decalcification; that micro-organisms destroy the enamel protein; or that keratolytic micro-organisms produce chelates that lead to decalcification. [NIH]

**Deoxyglucose:** 2-Deoxy-D-arabino-hexose. An antimetabolite of glucose with antiviral activity. [NIH]

**Depolarization:** The process or act of neutralizing polarity. In neurophysiology, the reversal of the resting potential in excitable cell membranes when stimulated, i.e., the tendency of the cell membrane potential to become positive with respect to the potential outside the cell. [EU]

**Dermal:** Pertaining to or coming from the skin. [NIH]

**Dermatitis:** Any inflammation of the skin. [NIH]

**Dermis:** A layer of vascular connective tissue underneath the epidermis. The surface of the dermis contains sensitive papillae. Embedded in or beneath the dermis are sweat glands, hair follicles, and sebaceous glands. [NIH]

**Developed Countries:** Countries that have reached a level of economic achievement through an increase of production, per capita income and consumption, and utilization of natural and human resources. [NIH]

**Developmental Biology:** The field of biology which deals with the process of the growth and differentiation of an organism. [NIH]

**Diabetes Mellitus:** A heterogeneous group of disorders that share glucose intolerance in common. [NIH]

**Diabetic Foot:** Ulcers of the foot as a complication of diabetes. Diabetic foot, often with

infection, is a common serious complication of diabetes and may require hospitalization and disfiguring surgery. The foot ulcers are probably secondary to neuropathies and vascular problems. [NIH]

**Diabetic Ketoacidosis:** Complication of diabetes resulting from severe insulin deficiency coupled with an absolute or relative increase in glucagon concentration. The metabolic acidosis is caused by the breakdown of adipose stores and resulting increased levels of free fatty acids. Glucagon accelerates the oxidation of the free fatty acids producing excess ketone bodies (ketosis). [NIH]

**Diagnostic procedure:** A method used to identify a disease. [NIH]

**Dialyzer:** A part of the hemodialysis machine. (See hemodialysis under dialysis.) The dialyzer has two sections separated by a membrane. One section holds dialysate. The other holds the patient's blood. [NIH]

**Diarrhea:** Passage of excessively liquid or excessively frequent stools. [NIH]

**Diastolic:** Of or pertaining to the diastole. [EU]

**Didanosine:** A dideoxynucleoside compound in which the 3'-hydroxy group on the sugar moiety has been replaced by a hydrogen. This modification prevents the formation of phosphodiester linkages which are needed for the completion of nucleic acid chains. Didanosine is a potent inhibitor of HIV replication, acting as a chain-terminator of viral DNA by binding to reverse transcriptase; ddI is then metabolized to dideoxyadenosine triphosphate, its putative active metabolite. [NIH]

**Dideoxyadenosine:** A dideoxynucleoside compound in which the 3'-hydroxy group on the sugar moiety has been replaced by a hydrogen. This modification prevents the formation of phosphodiester linkages which are needed for the completion of nucleic acid chains. The compound is an inhibitor of HIV replication, acting as a chain-terminator of viral DNA by binding to reverse transcriptase. Its principal side effect is nephrotoxicity. In vivo, dideoxyadenosine is rapidly metabolized to didanosine (ddI) by enzymatic deamination; ddI is then converted to dideoxyinosine monophosphate and ultimately to dideoxyadenosine triphosphate, the putative active metabolite. [NIH]

**Diencephalon:** The paired caudal parts of the prosencephalon from which the thalamus, hypothalamus, epithalamus, and subthalamus are derived. [NIH]

**Dietary Fats:** Fats present in food, especially in animal products such as meat, meat products, butter, ghee. They are present in lower amounts in nuts, seeds, and avocados. [NIH]

**Diethylcarbamazine:** An anthelmintic used primarily as the citrate in the treatment of filariasis, particularly infestations with Wucheria bancrofti or Loa loa. [NIH]

**Digestion:** The process of breakdown of food for metabolism and use by the body. [NIH]

**Digestive system:** The organs that take in food and turn it into products that the body can use to stay healthy. Waste products the body cannot use leave the body through bowel movements. The digestive system includes the salivary glands, mouth, esophagus, stomach, liver, pancreas, gallbladder, small and large intestines, and rectum. [NIH]

**Digestive tract:** The organs through which food passes when food is eaten. These organs are the mouth, esophagus, stomach, small and large intestines, and rectum. [NIH]

**Dihydrotestosterone:** Anabolic agent. [NIH]

**Dimethyl:** A volatile metabolite of the amino acid methionine. [NIH]

**Dimethyl Sulfoxide:** A highly polar organic liquid, that is used widely as a chemical solvent. Because of its ability to penetrate biological membranes, it is used as a vehicle for topical application of pharmaceuticals. It is also used to protect tissue during

cryopreservation. Dimethyl sulfoxide shows a range of pharmacological activity including analgesia and anti-inflammation. [NIH]

**Direct:** 1. Straight; in a straight line. 2. Performed immediately and without the intervention of subsidiary means. [EU]

**Discrete:** Made up of separate parts or characterized by lesions which do not become blended; not running together; separate. [NIH]

**Disease-Free Survival:** Period after successful treatment in which there is no appearance of the symptoms or effects of the disease. [NIH]

**Dissection:** Cutting up of an organism for study. [NIH]

**Disseminated sclerosis:** Hardening of tissue due to inflammation. [NIH]

**Dissociation:** 1. The act of separating or state of being separated. 2. The separation of a molecule into two or more fragments (atoms, molecules, ions, or free radicals) produced by the absorption of light or thermal energy or by solvation. 3. In psychology, a defense mechanism in which a group of mental processes are segregated from the rest of a person's mental activity in order to avoid emotional distress, as in the dissociative disorders (q.v.), or in which an idea or object is segregated from its emotional significance; in the first sense it is roughly equivalent to splitting, in the second, to isolation. 4. A defect of mental integration in which one or more groups of mental processes become separated off from normal consciousness and, thus separated, function as a unitary whole. [EU]

**Distal:** Remote; farther from any point of reference; opposed to proximal. In dentistry, used to designate a position on the dental arch farther from the median line of the jaw. [EU]

**Dizziness:** An imprecise term which may refer to a sense of spatial disorientation, motion of the environment, or lightheadedness. [NIH]

**Docetaxel:** An anticancer drug that belongs to the family of drugs called mitotic inhibitors. [NIH]

**Dopa:** The racemic or DL form of DOPA, an amino acid found in various legumes. The dextro form has little physiologic activity but the levo form (levodopa) is a very important physiologic mediator and precursor and pharmacological agent. [NIH]

**Dopamine:** An endogenous catecholamine and prominent neurotransmitter in several systems of the brain. In the synthesis of catecholamines from tyrosine, it is the immediate precursor to norepinephrine and epinephrine. Dopamine is a major transmitter in the extrapyramidal system of the brain, and important in regulating movement. A family of dopaminergic receptor subtypes mediate its action. Dopamine is used pharmacologically for its direct (beta adrenergic agonist) and indirect (adrenergic releasing) sympathomimetic effects including its actions as an inotropic agent and as a renal vasodilator. [NIH]

**Dorsal:** 1. Pertaining to the back or to any dorsum. 2. Denoting a position more toward the back surface than some other object of reference; same as posterior in human anatomy; superior in the anatomy of quadrupeds. [EU]

**Dosage Forms:** Completed forms of the pharmaceutical preparation in which prescribed doses of medication are included. They are designed to resist action by gastric fluids, prevent vomiting and nausea, reduce or alleviate the undesirable taste and smells associated with oral administration, achieve a high concentration of drug at target site, or produce a delayed or long-acting drug effect. They include capsules, liniments, ointments, pharmaceutical solutions, powders, tablets, etc. [NIH]

**Dose-dependent:** Refers to the effects of treatment with a drug. If the effects change when the dose of the drug is changed, the effects are said to be dose dependent. [NIH]

**Dose-limiting:** Describes side effects of a drug or other treatment that are serious enough to

prevent an increase in dose or level of that treatment. [NIH]

**Double-blind:** Pertaining to a clinical trial or other experiment in which neither the subject nor the person administering treatment knows which treatment any particular subject is receiving. [EU]

**Doxorubicin:** Antineoplastic antibiotic obtained from Streptomyces peucetics. It is a hydroxy derivative of daunorubicin and is used in treatment of both leukemia and solid tumors. [NIH]

**Drug Carriers:** Substances that facilitate time-controlled delivery, organ-specific targeting, protection, prolonged in vivo function, and decrease of toxicity of drugs. Liposomes, albumin microspheres, soluble synthetic polymers, DNA complexes, protein-drug conjugates, and carrier erythrocytes among others have been employed as biodegradable drug carriers. [NIH]

**Drug Costs:** The amount that a health care institution or organization pays for its drugs. It is one component of the final price that is charged to the consumer (fees, pharmaceutical or prescription fees). [NIH]

**Drug Design:** The molecular designing of drugs for specific purposes (such as DNA-binding, enzyme inhibition, anti-cancer efficacy, etc.) based on knowledge of molecular properties such as activity of functional groups, molecular geometry, and electronic structure, and also on information cataloged on analogous molecules. Drug design is generally computer-assisted molecular modeling and does not include pharmacokinetics, dosage analysis, or drug administration analysis. [NIH]

**Drug Interactions:** The action of a drug that may affect the activity, metabolism, or toxicity of another drug. [NIH]

**Drug Resistance:** Diminished or failed response of an organism, disease or tissue to the intended effectiveness of a chemical or drug. It should be differentiated from drug tolerance which is the progressive diminution of the susceptibility of a human or animal to the effects of a drug, as a result of continued administration. [NIH]

**Drug Tolerance:** Progressive diminution of the susceptibility of a human or animal to the effects of a drug, resulting from its continued administration. It should be differentiated from drug resistance wherein an organism, disease, or tissue fails to respond to the intended effectiveness of a chemical or drug. It should also be differentiated from maximum tolerated dose and no-observed-adverse-effect level. [NIH]

**Duodenum:** The first part of the small intestine. [NIH]

**Dyes:** Chemical substances that are used to stain and color other materials. The coloring may or may not be permanent. Dyes can also be used as therapeutic agents and test reagents in medicine and scientific research. [NIH]

**Dyskinesia:** Impairment of the power of voluntary movement, resulting in fragmentary or incomplete movements. [EU]

**Dyspepsia:** Impaired digestion, especially after eating. [NIH]

**Dysplasia:** Cells that look abnormal under a microscope but are not cancer. [NIH]

**Dyspnea:** Difficult or labored breathing. [NIH]

**Dyspnoea:** Difficult or laboured breathing. [EU]

**Dystonia:** Disordered tonicity of muscle. [EU]

**Dystrophy:** Any disorder arising from defective or faulty nutrition, especially the muscular dystrophies. [EU]

**Eczema:** A pruritic papulovesicular dermatitis occurring as a reaction to many endogenous

and exogenous agents (Dorland, 27th ed). [NIH]

**Edema:** Excessive amount of watery fluid accumulated in the intercellular spaces, most commonly present in subcutaneous tissue. [NIH]

**Effector:** It is often an enzyme that converts an inactive precursor molecule into an active second messenger. [NIH]

**Efferent:** Nerve fibers which conduct impulses from the central nervous system to muscles and glands. [NIH]

**Efficacy:** The extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under ideal conditions. Ideally, the determination of efficacy is based on the results of a randomized control trial. [NIH]

**Elasticity:** Resistance and recovery from distortion of shape. [NIH]

**Elastin:** The protein that gives flexibility to tissues. [NIH]

**Elective:** Subject to the choice or decision of the patient or physician; applied to procedures that are advantageous to the patient but not urgent. [EU]

**Electroacupuncture:** A form of acupuncture using low frequency electrically stimulated needles to produce analgesia and anesthesia and to treat disease. [NIH]

**Electrode:** Component of the pacing system which is at the distal end of the lead. It is the interface with living cardiac tissue across which the stimulus is transmitted. [NIH]

**Electrodiagnosis:** Diagnosis of disease states by recording the spontaneous electrical activity of tissues or organs or by the response to stimulation of electrically excitable tissue. [NIH]

**Electrolysis:** Destruction by passage of a galvanic electric current, as in disintegration of a chemical compound in solution. [NIH]

**Electrolyte:** A substance that dissociates into ions when fused or in solution, and thus becomes capable of conducting electricity; an ionic solute. [EU]

**Electromyography:** Recording of the changes in electric potential of muscle by means of surface or needle electrodes. [NIH]

**Electrophysiological:** Pertaining to electrophysiology, that is a branch of physiology that is concerned with the electric phenomena associated with living bodies and involved in their functional activity. [EU]

**Electroshock:** Induction of a stress reaction in experimental subjects by means of an electrical shock; applies to either convulsive or non-convulsive states. [NIH]

**Embryo:** The prenatal stage of mammalian development characterized by rapid morphological changes and the differentiation of basic structures. [NIH]

**Encephalopathy:** A disorder of the brain that can be caused by disease, injury, drugs, or chemicals. [NIH]

**Endemic:** Present or usually prevalent in a population or geographical area at all times; said of a disease or agent. Called also endemial. [EU]

**Endogenous:** Produced inside an organism or cell. The opposite is external (exogenous) production. [NIH]

**Endopeptidases:** A subclass of peptide hydrolases. They are classified primarily by their catalytic mechanism. Specificity is used only for identification of individual enzymes. They comprise the serine endopeptidases, EC 3.4.21; cysteine endopeptidases, EC 3.4.22; aspartic endopeptidases, EC 3.4.23, metalloendopeptidases, EC 3.4.24; and a group of enzymes yet to be assigned to any of the above sub-classes, EC 3.4.99. EC 3.4.-. [NIH]

**Endorphin:** Opioid peptides derived from beta-lipotropin. Endorphin is the most potent

naturally occurring analgesic agent. It is present in pituitary, brain, and peripheral tissues. [NIH]

**Endothelial cell:** The main type of cell found in the inside lining of blood vessels, lymph vessels, and the heart. [NIH]

**Endotoxins:** Toxins closely associated with the living cytoplasm or cell wall of certain microorganisms, which do not readily diffuse into the culture medium, but are released upon lysis of the cells. [NIH]

**End-stage renal:** Total chronic kidney failure. When the kidneys fail, the body retains fluid and harmful wastes build up. A person with ESRD needs treatment to replace the work of the failed kidneys. [NIH]

**Enkephalins:** One of the three major families of endogenous opioid peptides. The enkephalins are pentapeptides that are widespread in the central and peripheral nervous systems and in the adrenal medulla. [NIH]

**Environmental Exposure:** The exposure to potentially harmful chemical, physical, or biological agents in the environment or to environmental factors that may include ionizing radiation, pathogenic organisms, or toxic chemicals. [NIH]

**Environmental Health:** The science of controlling or modifying those conditions, influences, or forces surrounding man which relate to promoting, establishing, and maintaining health. [NIH]

**Enzymatic:** Phase where enzyme cuts the precursor protein. [NIH]

**Enzyme:** A protein that speeds up chemical reactions in the body. [NIH]

**Eosinophil:** A polymorphonuclear leucocyte with large eosinophilic granules in its cytoplasm, which plays a role in hypersensitivity reactions. [NIH]

**Eosinophilic:** A condition found primarily in grinding workers caused by a reaction of the pulmonary tissue, in particular the eosinophilic cells, to dust that has entered the lung. [NIH]

**Epidemic:** Occurring suddenly in numbers clearly in excess of normal expectancy; said especially of infectious diseases but applied also to any disease, injury, or other health-related event occurring in such outbreaks. [EU]

**Epidemiologic Studies:** Studies designed to examine associations, commonly, hypothesized causal relations. They are usually concerned with identifying or measuring the effects of risk factors or exposures. The common types of analytic study are case-control studies, cohort studies, and cross-sectional studies. [NIH]

**Epidemiological:** Relating to, or involving epidemiology. [EU]

**Epidermal:** Pertaining to or resembling epidermis. Called also epidermic or epidermoid. [EU]

**Epidermis:** Nonvascular layer of the skin. It is made up, from within outward, of five layers: 1) basal layer (stratum basale epidermidis); 2) spinous layer (stratum spinosum epidermidis); 3) granular layer (stratum granulosum epidermidis); 4) clear layer (stratum lucidum epidermidis); and 5) horny layer (stratum corneum epidermidis). [NIH]

**Epigastric:** Having to do with the upper middle area of the abdomen. [NIH]

**Epinephrine:** The active sympathomimetic hormone from the adrenal medulla in most species. It stimulates both the alpha- and beta- adrenergic systems, causes systemic vasoconstriction and gastrointestinal relaxation, stimulates the heart, and dilates bronchi and cerebral vessels. It is used in asthma and cardiac failure and to delay absorption of local anesthetics. [NIH]

**Epirubicin:** An anthracycline antibiotic which is the 4'-epi-isomer of doxorubicin. The compound exerts its antitumor effects by interference with the synthesis and function of

DNA. Clinical studies indicate activity in breast cancer, non-Hodgkin's lymphomas, ovarian cancer, soft-tissue sarcomas, pancreatic cancer, gastric cancer, small-cell lung cancer and acute leukemia. It is equal in activity to doxorubicin but exhibits less acute toxicities and less cardiotoxicity. [NIH]

**Epithelial:** Refers to the cells that line the internal and external surfaces of the body. [NIH]

**Epithelial Cells:** Cells that line the inner and outer surfaces of the body. [NIH]

**Epitope:** A molecule or portion of a molecule capable of binding to the combining site of an antibody. For every given antigenic determinant, the body can construct a variety of antibody-combining sites, some of which fit almost perfectly, and others which barely fit. [NIH]

**Equinus Deformity:** Plantar declination of the foot. [NIH]

**Equipment and Supplies:** Expendable and nonexpendable equipment, supplies, apparatus, and instruments that are used in diagnostic, surgical, therapeutic, scientific, and experimental procedures. [NIH]

**Erectile:** The inability to get or maintain an erection for satisfactory sexual intercourse. Also called impotence. [NIH]

**Erection:** The condition of being made rigid and elevated; as erectile tissue when filled with blood. [EU]

**Erythrocytes:** Red blood cells. Mature erythrocytes are non-nucleated, biconcave disks containing hemoglobin whose function is to transport oxygen. [NIH]

**Erythropoietin:** Glycoprotein hormone, secreted chiefly by the kidney in the adult and the liver in the fetus, that acts on erythroid stem cells of the bone marrow to stimulate proliferation and differentiation. [NIH]

**Esophagus:** The muscular tube through which food passes from the throat to the stomach. [NIH]

**Essential Tremor:** A rhythmic, involuntary, purposeless, oscillating movement resulting from the alternate contraction and relaxation of opposing groups of muscles. [NIH]

**Estrogen:** One of the two female sex hormones. [NIH]

**Etoposide:** A semisynthetic derivative of podophyllotoxin that exhibits antitumor activity. Etoposide inhibits DNA synthesis by forming a complex with topoisomerase II and DNA. This complex induces breaks in double stranded DNA and prevents repair by topoisomerase II binding. Accumulated breaks in DNA prevent entry into the mitotic phase of cell division, and lead to cell death. Etoposide acts primarily in the G2 and S phases of the cell cycle. [NIH]

**Eukaryotic Cells:** Cells of the higher organisms, containing a true nucleus bounded by a nuclear membrane. [NIH]

**Evacuation:** An emptying, as of the bowels. [EU]

**Evoke:** The electric response recorded from the cerebral cortex after stimulation of a peripheral sense organ. [NIH]

**Evoked Potentials:** The electric response evoked in the central nervous system by stimulation of sensory receptors or some point on the sensory pathway leading from the receptor to the cortex. The evoked stimulus can be auditory, somatosensory, or visual, although other modalities have been reported. Event-related potentials is sometimes used synonymously with evoked potentials but is often associated with the execution of a motor, cognitive, or psychophysiological task, as well as with the response to a stimulus. [NIH]

**Excisional:** The surgical procedure of removing a tumor by cutting it out. The biopsy is then

examined under a microscope. [NIH]

**Excitability:** Property of a cardiac cell whereby, when the cell is depolarized to a critical level (called threshold), the membrane becomes permeable and a regenerative inward current causes an action potential. [NIH]

**Excitation:** An act of irritation or stimulation or of responding to a stimulus; the addition of energy, as the excitation of a molecule by absorption of photons. [EU]

**Excitatory:** When cortical neurons are excited, their output increases and each new input they receive while they are still excited raises their output markedly. [NIH]

**Excitotoxicity:** Excessive exposure to glutamate or related compounds can kill brain neurons, presumably by overstimulating them. [NIH]

**Excrete:** To get rid of waste from the body. [NIH]

**Exercise Therapy:** Motion of the body or its parts to relieve symptoms or to improve function, leading to physical fitness, but not physical education and training. [NIH]

**Exocrine:** Secreting outwardly, via a duct. [EU]

**Exogenous:** Developed or originating outside the organism, as exogenous disease. [EU]

**Exon:** The part of the DNA that encodes the information for the actual amino acid sequence of the protein. In many eucaryotic genes, the coding sequences consist of a series of exons alternating with intron sequences. [NIH]

**Extensor:** A muscle whose contraction tends to straighten a limb; the antagonist of a flexor. [NIH]

**Extracellular:** Outside a cell or cells. [EU]

**Extracellular Matrix:** A meshwork-like substance found within the extracellular space and in association with the basement membrane of the cell surface. It promotes cellular proliferation and provides a supporting structure to which cells or cell lysates in culture dishes adhere. [NIH]

**Extrapyramidal:** Outside of the pyramidal tracts. [EU]

**Extravasation:** A discharge or escape, as of blood, from a vessel into the tissues. [EU]

**Extremity:** A limb; an arm or leg (membrum); sometimes applied specifically to a hand or foot. [EU]

**Eye Infections:** Infection, moderate to severe, caused by bacteria, fungi, or viruses, which occurs either on the external surface of the eye or intraocularly with probable inflammation, visual impairment, or blindness. [NIH]

**Facial:** Of or pertaining to the face. [EU]

**Family Planning:** Programs or services designed to assist the family in controlling reproduction by either improving or diminishing fertility. [NIH]

**Fasciculation:** A small local contraction of muscles, visible through the skin, representing a spontaneous discharge of a number of fibres innervated by a single motor nerve filament. [EU]

**Fascioliasis:** Helminth infection of the liver caused by species of Fasciola. [NIH]

**Fat:** Total lipids including phospholipids. [NIH]

**Fatty acids:** A major component of fats that are used by the body for energy and tissue development. [NIH]

**Feces:** The excrement discharged from the intestines, consisting of bacteria, cells exfoliated from the intestines, secretions, chiefly of the liver, and a small amount of food residue. [EU]

**Fees, Pharmaceutical:** Amounts charged to the patient or third-party payer for medication. It includes the pharmacist's professional fee and cost of ingredients, containers, etc. [NIH]

**Fetoprotein:** Transabdominal aspiration of fluid from the amniotic sac with a view to detecting increases of alpha-fetoprotein in maternal blood during pregnancy, as this is an important indicator of open neural tube defects in the fetus. [NIH]

**Fetus:** The developing offspring from 7 to 8 weeks after conception until birth. [NIH]

**Fibril:** Most bacterial viruses have a hollow tail with specialized fibrils at its tip. The tail fibers attach to the cell wall of the host. [NIH]

**Fibrin:** A protein derived from fibrinogen in the presence of thrombin, which forms part of the blood clot. [NIH]

**Fibrinogen:** Plasma glycoprotein clotted by thrombin, composed of a dimer of three non-identical pairs of polypeptide chains (alpha, beta, gamma) held together by disulfide bonds. Fibrinogen clotting is a sol-gel change involving complex molecular arrangements: whereas fibrinogen is cleaved by thrombin to form polypeptides A and B, the proteolytic action of other enzymes yields different fibrinogen degradation products. [NIH]

**Fibroblasts:** Connective tissue cells which secrete an extracellular matrix rich in collagen and other macromolecules. [NIH]

**Fibrosis:** Any pathological condition where fibrous connective tissue invades any organ, usually as a consequence of inflammation or other injury. [NIH]

**Fibrositis:** Aching, soreness or stiffness of muscles; often caused by inexpedient work postures. [NIH]

**Fissure:** Any cleft or groove, normal or otherwise; especially a deep fold in the cerebral cortex which involves the entire thickness of the brain wall. [EU]

**Flexor:** Muscles which flex a joint. [NIH]

**Flow Cytometry:** Technique using an instrument system for making, processing, and displaying one or more measurements on individual cells obtained from a cell suspension. Cells are usually stained with one or more fluorescent dyes specific to cell components of interest, e.g., DNA, and fluorescence of each cell is measured as it rapidly transverses the excitation beam (laser or mercury arc lamp). Fluorescence provides a quantitative measure of various biochemical and biophysical properties of the cell, as well as a basis for cell sorting. Other measurable optical parameters include light absorption and light scattering, the latter being applicable to the measurement of cell size, shape, density, granularity, and stain uptake. [NIH]

**Fludarabine:** An anticancer drug that belongs to the family of drugs called antimetabolites. [NIH]

**Fluorescence:** The property of emitting radiation while being irradiated. The radiation emitted is usually of longer wavelength than that incident or absorbed, e.g., a substance can be irradiated with invisible radiation and emit visible light. X-ray fluorescence is used in diagnosis. [NIH]

**Fluorescent Dyes:** Dyes that emit light when exposed to light. The wave length of the emitted light is usually longer than that of the incident light. Fluorochromes are substances that cause fluorescence in other substances, i.e., dyes used to mark or label other compounds with fluorescent tags. They are used as markers in biochemistry and immunology. [NIH]

**Fluorine:** A nonmetallic, diatomic gas that is a trace element and member of the halogen family. It is used in dentistry as flouride to prevent dental caries. [NIH]

**Folate:** A B-complex vitamin that is being studied as a cancer prevention agent. Also called folic acid. [NIH]

**Fold:** A plication or doubling of various parts of the body. [NIH]

**Folic Acid:** N-(4-(((2-Amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl)amino)benzoyl)-L-glutamic acid. A member of the vitamin B family that stimulates the hematopoietic system. It is present in the liver and kidney and is found in mushrooms, spinach, yeast, green leaves, and grasses. Folic acid is used in the treatment and prevention of folate deficiencies and megaloblastic anemia. [NIH]

**Foot Care:** Taking special steps to avoid foot problems such as sores, cuts, bunions, and calluses. Good care includes daily examination of the feet, toes, and toenails and choosing shoes and socks or stockings that fit well. People with diabetes have to take special care of their feet because nerve damage and reduced blood flow sometimes mean they will have less feeling in their feet than normal. They may not notice cuts and other problems as soon as they should. [NIH]

**Foot Ulcer:** Lesion on the surface of the skin of the foot, usually accompanied by inflammation. The lesion may become infected or necrotic and is frequently associated with diabetes or leprosy. [NIH]

**Forearm:** The part between the elbow and the wrist. [NIH]

**Free Radicals:** Highly reactive molecules with an unsatisfied electron valence pair. Free radicals are produced in both normal and pathological processes. They are proven or suspected agents of tissue damage in a wide variety of circumstances including radiation, damage from environment chemicals, and aging. Natural and pharmacological prevention of free radical damage is being actively investigated. [NIH]

**Friction:** Surface resistance to the relative motion of one body against the rubbing, sliding, rolling, or flowing of another with which it is in contact. [NIH]

**Fungi:** A kingdom of eukaryotic, heterotrophic organisms that live as saprobes or parasites, including mushrooms, yeasts, smuts, molds, etc. They reproduce either sexually or asexually, and have life cycles that range from simple to complex. Filamentous fungi refer to those that grow as multicelluar colonies (mushrooms and molds). [NIH]

**Fungus:** A general term used to denote a group of eukaryotic protists, including mushrooms, yeasts, rusts, moulds, smuts, etc., which are characterized by the absence of chlorophyll and by the presence of a rigid cell wall composed of chitin, mannans, and sometimes cellulose. They are usually of simple morphological form or show some reversible cellular specialization, such as the formation of pseudoparenchymatous tissue in the fruiting body of a mushroom. The dimorphic fungi grow, according to environmental conditions, as moulds or yeasts. [EU]

**Gait:** Manner or style of walking. [NIH]

**Galanin:** A neurotransmitter. [NIH]

**Gallbladder:** The pear-shaped organ that sits below the liver. Bile is concentrated and stored in the gallbladder. [NIH]

**Gamma-Endorphin:** An endogenous opioid peptide derived from the pro-opiomelanocortin precursor peptide. It differs from alpha-endorphin by one amino acid. [NIH]

**Ganglia:** Clusters of multipolar neurons surrounded by a capsule of loosely organized connective tissue located outside the central nervous system. [NIH]

**Ganglion:** 1. A knot, or knotlike mass. 2. A general term for a group of nerve cell bodies located outside the central nervous system; occasionally applied to certain nuclear groups within the brain or spinal cord, e.g. basal ganglia. 3. A benign cystic tumour occurring on a aponeurosis or tendon, as in the wrist or dorsum of the foot; it consists of a thin fibrous capsule enclosing a clear mucinous fluid. [EU]

**Ganglioside:** Protein kinase C's inhibitor which reduces ischemia-related brain damage. [NIH]

**Gap Junctions:** Connections between cells which allow passage of small molecules and electric current. Gap junctions were first described anatomically as regions of close apposition between cells with a narrow (1-2 nm) gap between cell membranes. The variety in the properties of gap junctions is reflected in the number of connexins, the family of proteins which form the junctions. [NIH]

**Gas:** Air that comes from normal breakdown of food. The gases are passed out of the body through the rectum (flatus) or the mouth (burp). [NIH]

**Gastric:** Having to do with the stomach. [NIH]

**Gastric Emptying:** The evacuation of food from the stomach into the duodenum. [NIH]

**Gastrin:** A hormone released after eating. Gastrin causes the stomach to produce more acid. [NIH]

**Gastrointestinal:** Refers to the stomach and intestines. [NIH]

**Gastrointestinal tract:** The stomach and intestines. [NIH]

**Gelatin:** A product formed from skin, white connective tissue, or bone collagen. It is used as a protein food adjuvant, plasma substitute, hemostatic, suspending agent in pharmaceutical preparations, and in the manufacturing of capsules and suppositories. [NIH]

**Gemcitabine:** An anticancer drug that belongs to the family of drugs called antimetabolites. [NIH]

**Gene:** The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein. [NIH]

**Gene Deletion:** A genetic rearrangement through loss of segments of DNA or RNA, bringing sequences which are normally separated into close proximity. This deletion may be detected using cytogenetic techniques and can also be inferred from the phenotype, indicating a deletion at one specific locus. [NIH]

**Gene Dosage:** The number of copies of a given gene present in a cell or nucleus. An increase in gene dosage can result in the formation of higher levels of gene product, provided that the gene is not subject to autogenous regulation. [NIH]

**Gene Expression:** The phenotypic manifestation of a gene or genes by the processes of gene action. [NIH]

**Gene Library:** A large collection of cloned DNA fragments from a given organism, tissue, organ, or cell type. It may contain complete genomic sequences (genomic library) or complementary DNA sequences, the latter being formed from messenger RNA and lacking intron sequences. [NIH]

**Gene Therapy:** The introduction of new genes into cells for the purpose of treating disease by restoring or adding gene expression. Techniques include insertion of retroviral vectors, transfection, homologous recombination, and injection of new genes into the nuclei of single cell embryos. The entire gene therapy process may consist of multiple steps. The new genes may be introduced into proliferating cells in vivo (e.g., bone marrow) or in vitro (e.g., fibroblast cultures) and the modified cells transferred to the site where the gene expression is required. Gene therapy may be particularly useful for treating enzyme deficiency diseases, hemoglobinopathies, and leukemias and may also prove useful in restoring drug sensitivity, particularly for leukemia. [NIH]

**Genetic Code:** The specifications for how information, stored in nucleic acid sequence (base sequence), is translated into protein sequence (amino acid sequence). The start, stop, and

order of amino acids of a protein is specified by consecutive triplets of nucleotides called codons (codon). [NIH]

**Genetic Engineering:** Directed modification of the gene complement of a living organism by such techniques as altering the DNA, substituting genetic material by means of a virus, transplanting whole nuclei, transplanting cell hybrids, etc. [NIH]

**Genetics:** The biological science that deals with the phenomena and mechanisms of heredity. [NIH]

**Genital:** Pertaining to the genitalia. [EU]

**Genomic Library:** A form of gene library containing the complete DNA sequences present in the genome of a given organism. It contrasts with a cDNA library which contains only sequences utilized in protein coding (lacking introns). [NIH]

**Genotype:** The genetic constitution of the individual; the characterization of the genes. [NIH]

**Germ Cells:** The reproductive cells in multicellular organisms. [NIH]

**Giardiasis:** An infection of the small intestine caused by the flagellated protozoan Giardia lamblia. It is spread via contaminated food and water and by direct person-to-person contact. [NIH]

**Ginkgo biloba:** Exclusive species of the genus Ginkgo, family Ginkgoacea. It produces extracts of medicinal interest. Ginkgo may refer to the genus or species. [NIH]

**Gland:** An organ that produces and releases one or more substances for use in the body. Some glands produce fluids that affect tissues or organs. Others produce hormones or participate in blood production. [NIH]

**Glucocorticoid:** A compound that belongs to the family of compounds called corticosteroids (steroids). Glucocorticoids affect metabolism and have anti-inflammatory and immunosuppressive effects. They may be naturally produced (hormones) or synthetic (drugs). [NIH]

**Gluconeogenesis:** The process by which glucose is formed from a non-carbohydrate source. [NIH]

**Glucose:** D-Glucose. A primary source of energy for living organisms. It is naturally occurring and is found in fruits and other parts of plants in its free state. It is used therapeutically in fluid and nutrient replacement. [NIH]

**Glucose Intolerance:** A pathological state in which the fasting plasma glucose level is less than 140 mg per deciliter and the 30-, 60-, or 90-minute plasma glucose concentration following a glucose tolerance test exceeds 200 mg per deciliter. This condition is seen frequently in diabetes mellitus but also occurs with other diseases. [NIH]

**Glucose tolerance:** The power of the normal liver to absorb and store large quantities of glucose and the effectiveness of intestinal absorption of glucose. The glucose tolerance test is a metabolic test of carbohydrate tolerance that measures active insulin, a hepatic function based on the ability of the liver to absorb glucose. The test consists of ingesting 100 grams of glucose into a fasting stomach; blood sugar should return to normal in 2 to 21 hours after ingestion. [NIH]

**Glucose Tolerance Test:** Determination of whole blood or plasma sugar in a fasting state before and at prescribed intervals (usually 1/2 hr, 1 hr, 3 hr, 4 hr) after taking a specified amount (usually 100 gm orally) of glucose. [NIH]

**Glutamate:** Excitatory neurotransmitter of the brain. [NIH]

**Glutamic Acid:** A non-essential amino acid naturally occurring in the L-form. Glutamic acid (glutamate) is the most common excitatory neurotransmitter in the central nervous system. [NIH]

**Glutamine:** A non-essential amino acid present abundantly throught the body and is involved in many metabolic processes. It is synthesized from glutamic acid and ammonia. It is the principal carrier of nitrogen in the body and is an important energy source for many cells. [NIH]

**Glutathione Peroxidase:** An enzyme catalyzing the oxidation of 2 moles of glutathione in the presence of hydrogen peroxide to yield oxidized glutathione and water. EC 1.11.1.9. [NIH]

**Glycine:** A non-essential amino acid. It is found primarily in gelatin and silk fibroin and used therapeutically as a nutrient. It is also a fast inhibitory neurotransmitter. [NIH]

**Glycogen:** A sugar stored in the liver and muscles. It releases glucose into the blood when cells need it for energy. Glycogen is the chief source of stored fuel in the body. [NIH]

**Glycoprotein:** A protein that has sugar molecules attached to it. [NIH]

**Glycosaminoglycans:** Heteropolysaccharides which contain an N-acetylated hexosamine in a characteristic repeating disaccharide unit. The repeating structure of each disaccharide involves alternate 1,4- and 1,3-linkages consisting of either N-acetylglucosamine or N-acetylgalactosamine. [NIH]

**Glycosidic:** Formed by elimination of water between the anomeric hydroxyl of one sugar and a hydroxyl of another sugar molecule. [NIH]

**Glycosuria:** The presence of glucose in the urine; especially the excretion of an abnormally large amount of sugar (glucose) in the urine, i.e., more than 1 gm. in 24 hours. [EU]

**Glycosylation:** The chemical or biochemical addition of carbohydrate or glycosyl groups to other chemicals, especially peptides or proteins. Glycosyl transferases are used in this biochemical reaction. [NIH]

**Gonadal:** Pertaining to a gonad. [EU]

**Gout:** Hereditary metabolic disorder characterized by recurrent acute arthritis, hyperuricemia and deposition of sodium urate in and around the joints, sometimes with formation of uric acid calculi. [NIH]

**Governing Board:** The group in which legal authority is vested for the control of health-related institutions and organizations. [NIH]

**Grade:** The grade of a tumor depends on how abnormal the cancer cells look under a microscope and how quickly the tumor is likely to grow and spread. Grading systems are different for each type of cancer. [NIH]

**Graft:** Healthy skin, bone, or other tissue taken from one part of the body and used to replace diseased or injured tissue removed from another part of the body. [NIH]

**Granulocyte:** A type of white blood cell that fights bacterial infection. Neutrophils, eosinophils, and basophils are granulocytes. [NIH]

**Granulocytopenia:** A deficiency in the number of granulocytes, a type of white blood cell. [NIH]

**Granulomas:** Small lumps in tissues caused by inflammation. [NIH]

**Grasses:** A large family, Gramineae, of narrow-leaved herbaceous monocots. Many grasses produce highly allergenic pollens and are hosts to cattle parasites and toxic fungi. [NIH]

**Gravis:** Eruption of watery blisters on the skin among those handling animals and animal products. [NIH]

**Growth:** The progressive development of a living being or part of an organism from its earliest stage to maturity. [NIH]

**Growth factors:** Substances made by the body that function to regulate cell division and cell

survival. Some growth factors are also produced in the laboratory and used in biological therapy. [NIH]

**Guanine:** One of the four DNA bases. [NIH]

**Haemodialysis:** The removal of certain elements from the blood by virtue of the difference in the rates of their diffusion through a semipermeable membrane, e.g., by means of a haemodialyzer. [EU]

**Hair Cells:** Mechanoreceptors located in the organ of Corti that are sensitive to auditory stimuli and in the vestibular apparatus that are sensitive to movement of the head. In each case the accessory sensory structures are arranged so that appropriate stimuli cause movement of the hair-like projections (stereocilia and kinocilia) which relay the information centrally in the nervous system. [NIH]

**Haptens:** Small antigenic determinants capable of eliciting an immune response only when coupled to a carrier. Haptens bind to antibodies but by themselves cannot elicit an antibody response. [NIH]

**Headache:** Pain in the cranial region that may occur as an isolated and benign symptom or as a manifestation of a wide variety of conditions including subarachnoid hemorrhage; craniocerebral trauma; central nervous system infections; intracranial hypertension; and other disorders. In general, recurrent headaches that are not associated with a primary disease process are referred to as headache disorders (e.g., migraine). [NIH]

**Headache Disorders:** Common conditions characterized by persistent or recurrent headaches. Headache syndrome classification systems may be based on etiology (e.g., vascular headache, post-traumatic headaches, etc.), temporal pattern (e.g., cluster headache, paroxysmal hemicrania, etc.), and precipitating factors (e.g., cough headache). [NIH]

**Heartbeat:** One complete contraction of the heart. [NIH]

**Heartburn:** Substernal pain or burning sensation, usually associated with regurgitation of gastric juice into the esophagus. [NIH]

**Hematologic Diseases:** Disorders of the blood and blood forming tissues. [NIH]

**Heme:** The color-furnishing portion of hemoglobin. It is found free in tissues and as the prosthetic group in many hemeproteins. [NIH]

**Hemodialysis:** The use of a machine to clean wastes from the blood after the kidneys have failed. The blood travels through tubes to a dialyzer, which removes wastes and extra fluid. The cleaned blood then flows through another set of tubes back into the body. [NIH]

**Hemoglobin:** One of the fractions of glycosylated hemoglobin A1c. Glycosylated hemoglobin is formed when linkages of glucose and related monosaccharides bind to hemoglobin A and its concentration represents the average blood glucose level over the previous several weeks. HbA1c levels are used as a measure of long-term control of plasma glucose (normal, 4 to 6 percent). In controlled diabetes mellitus, the concentration of glycosylated hemoglobin A is within the normal range, but in uncontrolled cases the level may be 3 to 4 times the normal conentration. Generally, complications are substantially lower among patients with Hb levels of 7 percent or less than in patients with HbA1c levels of 9 percent or more. [NIH]

**Hemoglobinopathies:** A group of inherited disorders characterized by structural alterations within the hemoglobin molecule. [NIH]

**Hemoglobinuria:** The presence of free hemoglobin in the urine. [NIH]

**Hemorrhage:** Bleeding or escape of blood from a vessel. [NIH]

**Hemostasis:** The process which spontaneously arrests the flow of blood from vessels

carrying blood under pressure. It is accomplished by contraction of the vessels, adhesion and aggregation of formed blood elements, and the process of blood or plasma coagulation. [NIH]

**Hepatic:** Refers to the liver. [NIH]

**Hepatitis:** Inflammation of the liver and liver disease involving degenerative or necrotic alterations of hepatocytes. [NIH]

**Hepatocytes:** The main structural component of the liver. They are specialized epithelial cells that are organized into interconnected plates called lobules. [NIH]

**Heptanol:** A colorless liquid with a fragrant odor. It is used as an intermediate, solvent and in cosmetics. [NIH]

**Hereditary:** Of, relating to, or denoting factors that can be transmitted genetically from one generation to another. [NIH]

**Heredity:** 1. The genetic transmission of a particular quality or trait from parent to offspring. 2. The genetic constitution of an individual. [EU]

**Heterogeneity:** The property of one or more samples or populations which implies that they are not identical in respect of some or all of their parameters, e. g. heterogeneity of variance. [NIH]

**Heterogenic:** Derived from a different source or species. Also called heterogenous. [NIH]

**Heterogenous:** Derived from a different source or species. Also called heterogenic. [NIH]

**Hippocampus:** A curved elevation of gray matter extending the entire length of the floor of the temporal horn of the lateral ventricle (Dorland, 28th ed). The hippocampus, subiculum, and dentate gyrus constitute the hippocampal formation. Sometimes authors include the entorhinal cortex in the hippocampal formation. [NIH]

**Histamine:** 1H-Imidazole-4-ethanamine. A depressor amine derived by enzymatic decarboxylation of histidine. It is a powerful stimulant of gastric secretion, a constrictor of bronchial smooth muscle, a vasodilator, and also a centrally acting neurotransmitter. [NIH]

**Histidine:** An essential amino acid important in a number of metabolic processes. It is required for the production of histamine. [NIH]

**Histology:** The study of tissues and cells under a microscope. [NIH]

**Homologous:** Corresponding in structure, position, origin, etc., as (a) the feathers of a bird and the scales of a fish, (b) antigen and its specific antibody, (c) allelic chromosomes. [EU]

**Hormonal:** Pertaining to or of the nature of a hormone. [EU]

**Hormone:** A substance in the body that regulates certain organs. Hormones such as gastrin help in breaking down food. Some hormones come from cells in the stomach and small intestine. [NIH]

**Hormone Replacement Therapy:** Therapeutic use of hormones to alleviate the effects of hormone deficiency. [NIH]

**Hormone therapy:** Treatment of cancer by removing, blocking, or adding hormones. Also called endocrine therapy. [NIH]

**Host:** Any animal that receives a transplanted graft. [NIH]

**Houseflies:** Flies of the species Musca domestica (family muscidae), which infest human habitations throughout the world and often act as carriers of pathogenic organisms. [NIH]

**Human Development:** Continuous sequential changes which occur in the physiological and psychological functions during the individual's life. [NIH]

**Hybrid:** Cross fertilization between two varieties or, more usually, two species of vines, see

also crossing. [NIH]

**Hydrogen:** The first chemical element in the periodic table. It has the atomic symbol H, atomic number 1, and atomic weight 1. It exists, under normal conditions, as a colorless, odorless, tasteless, diatomic gas. Hydrogen ions are protons. Besides the common H1 isotope, hydrogen exists as the stable isotope deuterium and the unstable, radioactive isotope tritium. [NIH]

**Hydrolysis:** The process of cleaving a chemical compound by the addition of a molecule of water. [NIH]

**Hydrophilic:** Readily absorbing moisture; hygroscopic; having strongly polar groups that readily interact with water. [EU]

**Hydrophobic:** Not readily absorbing water, or being adversely affected by water, as a hydrophobic colloid. [EU]

**Hydroxylysine:** A hydroxylated derivative of the amino acid lysine that is present in certain collagens. [NIH]

**Hydroxyproline:** A hydroxylated form of the imino acid proline. A deficiency in ascorbic acid can result in impaired hydroxyproline formation. [NIH]

**Hydroxyurea:** An antineoplastic agent that inhibits DNA synthesis through the inhibition of ribonucleoside diphosphate reductase. [NIH]

**Hyperalgesia:** Excessive sensitiveness or sensibility to pain. [EU]

**Hyperbaric:** Characterized by greater than normal pressure or weight; applied to gases under greater than atmospheric pressure, as hyperbaric oxygen, or to a solution of greater specific gravity than another taken as a standard of reference. [EU]

**Hyperbaric oxygen:** Oxygen that is at an atmospheric pressure higher than the pressure at sea level. Breathing hyperbaric oxygen to enhance the effectiveness of radiation therapy is being studied. [NIH]

**Hyperglycaemia:** Abnormally increased content of sugar in the blood. [EU]

**Hyperglycemia:** Abnormally high blood sugar. [NIH]

**Hyperostosis:** Increase in the mass of bone per unit volume. [NIH]

**Hyperplasia:** An increase in the number of cells in a tissue or organ, not due to tumor formation. It differs from hypertrophy, which is an increase in bulk without an increase in the number of cells. [NIH]

**Hypersensitivity:** Altered reactivity to an antigen, which can result in pathologic reactions upon subsequent exposure to that particular antigen. [NIH]

**Hypertension:** Persistently high arterial blood pressure. Currently accepted threshold levels are 140 mm Hg systolic and 90 mm Hg diastolic pressure. [NIH]

**Hypertrophy:** General increase in bulk of a part or organ, not due to tumor formation, nor to an increase in the number of cells. [NIH]

**Hyperuricemia:** A buildup of uric acid (a byproduct of metabolism) in the blood; a side effect of some anticancer drugs. [NIH]

**Hypoglycaemia:** An abnormally diminished concentration of glucose in the blood, which may lead to tremulousness, cold sweat, piloerection, hypothermia, and headache, accompanied by irritability, confusion, hallucinations, bizarre behaviour, and ultimately, convulsions and coma. [EU]

**Hypoglycemia:** Abnormally low blood sugar [NIH]

**Hypoglycemic:** An orally active drug that produces a fall in blood glucose concentration.

[NIH]

**Hypoglycemic Agents:** Agents which lower the blood glucose level. [NIH]

**Hypokinesia:** Slow or diminished movement of body musculature. It may be associated with basal ganglia diseases; mental disorders; prolonged inactivity due to illness; experimental protocols used to evaluate the physiologic effects of immobility; and other conditions. [NIH]

**Hypoplasia:** Incomplete development or underdevelopment of an organ or tissue. [EU]

**Hypotension:** Abnormally low blood pressure. [NIH]

**Hypothalamus:** Ventral part of the diencephalon extending from the region of the optic chiasm to the caudal border of the mammillary bodies and forming the inferior and lateral walls of the third ventricle. [NIH]

**Hypothermia:** Lower than normal body temperature, especially in warm-blooded animals; in man usually accidental or unintentional. [NIH]

**Hypothyroidism:** Deficiency of thyroid activity. In adults, it is most common in women and is characterized by decrease in basal metabolic rate, tiredness and lethargy, sensitivity to cold, and menstrual disturbances. If untreated, it progresses to full-blown myxoedema. In infants, severe hypothyroidism leads to cretinism. In juveniles, the manifestations are intermediate, with less severe mental and developmental retardation and only mild symptoms of the adult form. When due to pituitary deficiency of thyrotropin secretion it is called secondary hypothyroidism. [EU]

**Hypotonia:** A condition of diminished tone of the skeletal muscles; diminished resistance of muscles to passive stretching. [EU]

**Hypoxanthine:** A purine and a reaction intermediate in the metabolism of adenosine and in the formation of nucleic acids by the salvage pathway. [NIH]

**Hypoxic:** Having too little oxygen. [NIH]

**Id:** The part of the personality structure which harbors the unconscious instinctive desires and strivings of the individual. [NIH]

**Idiopathic:** Describes a disease of unknown cause. [NIH]

**Ileus:** Obstruction of the intestines. [EU]

**Imidazole:** C3H4N2. The ring is present in polybenzimidazoles. [NIH]

**Immune response:** The activity of the immune system against foreign substances (antigens). [NIH]

**Immune system:** The organs, cells, and molecules responsible for the recognition and disposal of foreign ("non-self") material which enters the body. [NIH]

**Immunity:** Nonsusceptibility to the invasive or pathogenic effects of foreign microorganisms or to the toxic effect of antigenic substances. [NIH]

**Immunodeficiency:** The decreased ability of the body to fight infection and disease. [NIH]

**Immunodeficiency syndrome:** The inability of the body to produce an immune response. [NIH]

**Immunoglobulin:** A protein that acts as an antibody. [NIH]

**Immunologic:** The ability of the antibody-forming system to recall a previous experience with an antigen and to respond to a second exposure with the prompt production of large amounts of antibody. [NIH]

**Immunology:** The study of the body's immune system. [NIH]

**Immunophilin:** A drug for the treatment of Parkinson's disease. [NIH]

**Immunosuppressant:** An agent capable of suppressing immune responses. [EU]

**Impairment:** In the context of health experience, an impairment is any loss or abnormality of psychological, physiological, or anatomical structure or function. [NIH]

**Impotence:** The inability to perform sexual intercourse. [NIH]

**In situ:** In the natural or normal place; confined to the site of origin without invasion of neighbouring tissues. [EU]

**In Situ Hybridization:** A technique that localizes specific nucleic acid sequences within intact chromosomes, eukaryotic cells, or bacterial cells through the use of specific nucleic acid-labeled probes. [NIH]

**In vitro:** In the laboratory (outside the body). The opposite of in vivo (in the body). [NIH]

**In vivo:** In the body. The opposite of in vitro (outside the body or in the laboratory). [NIH]

**Incision:** A cut made in the body during surgery. [NIH]

**Incisor:** Anything adapted for cutting; any one of the four front teeth in each jaw. [NIH]

**Incontinence:** Inability to control the flow of urine from the bladder (urinary incontinence) or the escape of stool from the rectum (fecal incontinence). [NIH]

**Incubation:** The development of an infectious disease from the entrance of the pathogen to the appearance of clinical symptoms. [EU]

**Incubation period:** The period of time likely to elapse between exposure to the agent of the disease and the onset of clinical symptoms. [NIH]

**Indicative:** That indicates; that points out more or less exactly; that reveals fairly clearly. [EU]

**Indigestion:** Poor digestion. Symptoms include heartburn, nausea, bloating, and gas. Also called dyspepsia. [NIH]

**Induction:** The act or process of inducing or causing to occur, especially the production of a specific morphogenetic effect in the developing embryo through the influence of evocators or organizers, or the production of anaesthesia or unconsciousness by use of appropriate agents. [EU]

**Infarction:** A pathological process consisting of a sudden insufficient blood supply to an area, which results in necrosis of that area. It is usually caused by a thrombus, an embolus, or a vascular torsion. [NIH]

**Infection:** 1. Invasion and multiplication of microorganisms in body tissues, which may be clinically unapparent or result in local cellular injury due to competitive metabolism, toxins, intracellular replication, or antigen-antibody response. The infection may remain localized, subclinical, and temporary if the body's defensive mechanisms are effective. A local infection may persist and spread by extension to become an acute, subacute, or chronic clinical infection or disease state. A local infection may also become systemic when the microorganisms gain access to the lymphatic or vascular system. 2. An infectious disease. [EU]

**Infiltration:** The diffusion or accumulation in a tissue or cells of substances not normal to it or in amounts of the normal. Also, the material so accumulated. [EU]

**Inflammation:** A pathological process characterized by injury or destruction of tissues caused by a variety of cytologic and chemical reactions. It is usually manifested by typical signs of pain, heat, redness, swelling, and loss of function. [NIH]

**Inflammatory bowel disease:** A general term that refers to the inflammation of the colon and rectum. Inflammatory bowel disease includes ulcerative colitis and Crohn's disease. [NIH]

**Infusion:** A method of putting fluids, including drugs, into the bloodstream. Also called

intravenous infusion. [NIH]

**Ingestion:** Taking into the body by mouth [NIH]

**Inhalation:** The drawing of air or other substances into the lungs. [EU]

**Initiation:** Mutation induced by a chemical reactive substance causing cell changes; being a step in a carcinogenic process. [NIH]

**Inlay:** In dentistry, a filling first made to correspond with the form of a dental cavity and then cemented into the cavity. [NIH]

**Innervation:** 1. The distribution or supply of nerves to a part. 2. The supply of nervous energy or of nerve stimulus sent to a part. [EU]

**Inorganic:** Pertaining to substances not of organic origin. [EU]

**Inositol:** An isomer of glucose that has traditionally been considered to be a B vitamin although it has an uncertain status as a vitamin and a deficiency syndrome has not been identified in man. (From Martindale, The Extra Pharmacopoeia, 30th ed, p1379) Inositol phospholipids are important in signal transduction. [NIH]

**Inositol Phosphates:** Phosphoric acid esters of inositol. They include mono- and polyphosphoric acid esters, with the exception of inositol hexaphosphate which is phytic acid. [NIH]

**Inotropic:** Affecting the force or energy of muscular contractions. [EU]

**Insecticides:** Pesticides designed to control insects that are harmful to man. The insects may be directly harmful, as those acting as disease vectors, or indirectly harmful, as destroyers of crops, food products, or textile fabrics. [NIH]

**Insight:** The capacity to understand one's own motives, to be aware of one's own psychodynamics, to appreciate the meaning of symbolic behavior. [NIH]

**Insomnia:** Difficulty in going to sleep or getting enough sleep. [NIH]

**Insulator:** Material covering the metal conductor of the lead. It is usually polyurethane or silicone. [NIH]

**Insulin:** A protein hormone secreted by beta cells of the pancreas. Insulin plays a major role in the regulation of glucose metabolism, generally promoting the cellular utilization of glucose. It is also an important regulator of protein and lipid metabolism. Insulin is used as a drug to control insulin-dependent diabetes mellitus. [NIH]

**Insulin-dependent diabetes mellitus:** A disease characterized by high levels of blood glucose resulting from defects in insulin secretion, insulin action, or both. Autoimmune, genetic, and environmental factors are involved in the development of type I diabetes. [NIH]

**Insulin-like:** Muscular growth factor. [NIH]

**Interferon:** A biological response modifier (a substance that can improve the body's natural response to disease). Interferons interfere with the division of cancer cells and can slow tumor growth. There are several types of interferons, including interferon-alpha, -beta, and -gamma. These substances are normally produced by the body. They are also made in the laboratory for use in treating cancer and other diseases. [NIH]

**Interferon-alpha:** One of the type I interferons produced by peripheral blood leukocytes or lymphoblastoid cells when exposed to live or inactivated virus, double-stranded RNA, or bacterial products. It is the major interferon produced by virus-induced leukocyte cultures and, in addition to its pronounced antiviral activity, it causes activation of NK cells. [NIH]

**Intermediate Filaments:** Cytoplasmic filaments intermediate in diameter (about 10 nanometers) between the microfilaments and the microtubules. They may be composed of any of a number of different proteins and form a ring around the cell nucleus. [NIH]

**Intermittent:** Occurring at separated intervals; having periods of cessation of activity. [EU]

**Intervertebral:** Situated between two contiguous vertebrae. [EU]

**Intervertebral Disk Displacement:** An intervertebral disk in which the nucleus pulposus has protruded through surrounding fibrocartilage. This occurs most frequently in the lower lumbar region. [NIH]

**Intestinal:** Having to do with the intestines. [NIH]

**Intestines:** The section of the alimentary canal from the stomach to the anus. It includes the large intestine and small intestine. [NIH]

**Intoxication:** Poisoning, the state of being poisoned. [EU]

**Intracellular:** Inside a cell. [NIH]

**Intracellular Membranes:** Membranes of subcellular structures. [NIH]

**Intracranial Hypertension:** Increased pressure within the cranial vault. This may result from several conditions, including hydrocephalus; brain edema; intracranial masses; severe systemic hypertension; pseudotumor cerebri; and other disorders. [NIH]

**Intracranial Pressure:** Pressure within the cranial cavity. It is influenced by brain mass, the circulatory system, CSF dynamics, and skull rigidity. [NIH]

**Intramuscular:** IM. Within or into muscle. [NIH]

**Intramuscular injection:** IM. Injection into a muscle. [NIH]

**Intraperitoneal:** IP. Within the peritoneal cavity (the area that contains the abdominal organs). [NIH]

**Intravenous:** IV. Into a vein. [NIH]

**Intrinsic:** Situated entirely within or pertaining exclusively to a part. [EU]

**Introns:** Non-coding, intervening sequences of DNA that are transcribed, but are removed from within the primary gene transcript and rapidly degraded during maturation of messenger RNA. Most genes in the nuclei of eukaryotes contain introns, as do mitochondrial and chloroplast genes. [NIH]

**Invasive:** 1. Having the quality of invasiveness. 2. Involving puncture or incision of the skin or insertion of an instrument or foreign material into the body; said of diagnostic techniques. [EU]

**Involuntary:** Reaction occurring without intention or volition. [NIH]

**Ion Channels:** Gated, ion-selective glycoproteins that traverse membranes. The stimulus for channel gating can be a membrane potential, drug, transmitter, cytoplasmic messenger, or a mechanical deformation. Ion channels which are integral parts of ionotropic neurotransmitter receptors are not included. [NIH]

**Ionizing:** Radiation comprising charged particles, e. g. electrons, protons, alpha-particles, etc., having sufficient kinetic energy to produce ionization by collision. [NIH]

**Ions:** An atom or group of atoms that have a positive or negative electric charge due to a gain (negative charge) or loss (positive charge) of one or more electrons. Atoms with a positive charge are known as cations; those with a negative charge are anions. [NIH]

**Ischemia:** Deficiency of blood in a part, due to functional constriction or actual obstruction of a blood vessel. [EU]

**Islet:** Cell producing insulin in pancreas. [NIH]

**Isoenzyme:** Different forms of an enzyme, usually occurring in different tissues. The isoenzymes of a particular enzyme catalyze the same reaction but they differ in some of their

properties. [NIH]

**Isoleucine:** An essential branched-chain amino acid found in many proteins. It is an isomer of LEUCINE. It is important in hemoglobin synthesis and regulation of blood sugar and energy levels. [NIH]

**Isoniazid:** Antibacterial agent used primarily as a tuberculostatic. It remains the treatment of choice for tuberculosis. [NIH]

**Joint:** The point of contact between elements of an animal skeleton with the parts that surround and support it. [NIH]

**Kb:** A measure of the length of DNA fragments, 1 Kb = 1000 base pairs. The largest DNA fragments are up to 50 kilobases long. [NIH]

**Keratin:** A class of fibrous proteins or scleroproteins important both as structural proteins and as keys to the study of protein conformation. The family represents the principal constituent of epidermis, hair, nails, horny tissues, and the organic matrix of tooth enamel. Two major conformational groups have been characterized, alpha-keratin, whose peptide backbone forms an alpha-helix, and beta-keratin, whose backbone forms a zigzag or pleated sheet structure. [NIH]

**Keratinocytes:** Epidermal cells which synthesize keratin and undergo characteristic changes as they move upward from the basal layers of the epidermis to the cornified (horny) layer of the skin. Successive stages of differentiation of the keratinocytes forming the epidermal layers are basal cell, spinous or prickle cell, and the granular cell. [NIH]

**Keratoconjunctivitis:** Simultaneous inflammation of the cornea and conjunctiva. [NIH]

**Keratoconjunctivitis Sicca:** Drying and inflammation of the conjunctiva as a result of insufficient lacrimal secretion. When found in association with xerostomia and polyarthritis, it is called Sjogren's syndrome. [NIH]

**Ketoacidosis:** Acidosis accompanied by the accumulation of ketone bodies (ketosis) in the body tissues and fluids, as in diabetic acidosis. [EU]

**Ketone Bodies:** Chemicals that the body makes when there is not enough insulin in the blood and it must break down fat for its energy. Ketone bodies can poison and even kill body cells. When the body does not have the help of insulin, the ketones build up in the blood and then "spill" over into the urine so that the body can get rid of them. The body can also rid itself of one type of ketone, called acetone, through the lungs. This gives the breath a fruity odor. Ketones that build up in the body for a long time lead to serious illness and coma. [NIH]

**Ketosis:** A condition of having ketone bodies build up in body tissues and fluids. The signs of ketosis are nausea, vomiting, and stomach pain. Ketosis can lead to ketoacidosis. [NIH]

**Kidney Disease:** Any one of several chronic conditions that are caused by damage to the cells of the kidney. People who have had diabetes for a long time may have kidney damage. Also called nephropathy. [NIH]

**Kidney Failure:** The inability of a kidney to excrete metabolites at normal plasma levels under conditions of normal loading, or the inability to retain electrolytes under conditions of normal intake. In the acute form (kidney failure, acute), it is marked by uremia and usually by oliguria or anuria, with hyperkalemia and pulmonary edema. The chronic form (kidney failure, chronic) is irreversible and requires hemodialysis. [NIH]

**Kidney Failure, Acute:** A clinical syndrome characterized by a sudden decrease in glomerular filtration rate, often to values of less than 1 to 2 ml per minute. It is usually associated with oliguria (urine volumes of less than 400 ml per day) and is always associated with biochemical consequences of the reduction in glomerular filtration rate such as a rise in

blood urea nitrogen (BUN) and serum creatinine concentrations. [NIH]

**Kidney Failure, Chronic:** An irreversible and usually progressive reduction in renal function in which both kidneys have been damaged by a variety of diseases to the extent that they are unable to adequately remove the metabolic products from the blood and regulate the body's electrolyte composition and acid-base balance. Chronic kidney failure requires hemodialysis or surgery, usually kidney transplantation. [NIH]

**Kinetic:** Pertaining to or producing motion. [EU]

**Labile:** 1. Gliding; moving from point to point over the surface; unstable; fluctuating. 2. Chemically unstable. [EU]

**Lacrimal:** Pertaining to the tears. [EU]

**Laminin:** Large, noncollagenous glycoprotein with antigenic properties. It is localized in the basement membrane lamina lucida and functions to bind epithelial cells to the basement membrane. Evidence suggests that the protein plays a role in tumor invasion. [NIH]

**Lamivudine:** A reverse transcriptase inhibitor and zalcitabine analog in which a sulfur atom replaces the 3' carbon of the pentose ring. It is used to treat HIV disease. [NIH]

**Language Disorders:** Conditions characterized by deficiencies of comprehension or expression of written and spoken forms of language. These include acquired and developmental disorders. [NIH]

**Large Intestine:** The part of the intestine that goes from the cecum to the rectum. The large intestine absorbs water from stool and changes it from a liquid to a solid form. The large intestine is 5 feet long and includes the appendix, cecum, colon, and rectum. Also called colon. [NIH]

**Latent:** Phoria which occurs at one distance or another and which usually has no troublesome effect. [NIH]

**Lectin:** A complex molecule that has both protein and sugars. Lectins are able to bind to the outside of a cell and cause biochemical changes in it. Lectins are made by both animals and plants. [NIH]

**Lens:** The transparent, double convex (outward curve on both sides) structure suspended between the aqueous and vitreous; helps to focus light on the retina. [NIH]

**Lentivirus:** A genus of the family Retroviridae consisting of non-oncogenic retroviruses that produce multi-organ diseases characterized by long incubation periods and persistent infection. Lentiviruses are unique in that they contain open reading frames (ORFs) between the pol and env genes and in the 3' env region. Five serogroups are recognized, reflecting the mammalian hosts with which they are associated. HIV-1 is the type species. [NIH]

**Leprosy:** A chronic granulomatous infection caused by Mycobacterium leprae. The granulomatous lesions are manifested in the skin, the mucous membranes, and the peripheral nerves. Two polar or principal types are lepromatous and tuberculoid. [NIH]

**Lethargy:** Abnormal drowsiness or stupor; a condition of indifference. [EU]

**Leucocyte:** All the white cells of the blood and their precursors (myeloid cell series, lymphoid cell series) but commonly used to indicate granulocytes exclusive of lymphocytes. [NIH]

**Leukaemia:** An acute or chronic disease of unknown cause in man and other warm-blooded animals that involves the blood-forming organs, is characterized by an abnormal increase in the number of leucocytes in the tissues of the body with or without a corresponding increase of those in the circulating blood, and is classified according of the type leucocyte most prominently involved. [EU]

**Leukemia:** Cancer of blood-forming tissue. [NIH]

**Leukocytes:** White blood cells. These include granular leukocytes (basophils, eosinophils, and neutrophils) as well as non-granular leukocytes (lymphocytes and monocytes). [NIH]

**Leukocytosis:** A transient increase in the number of leukocytes in a body fluid. [NIH]

**Leukoencephalopathy:** A condition with spongy holes in the brain's white matter. [NIH]

**Leukopenia:** A condition in which the number of leukocytes (white blood cells) in the blood is reduced. [NIH]

**Levodopa:** The naturally occurring form of dopa and the immediate precursor of dopamine. Unlike dopamine itself, it can be taken orally and crosses the blood-brain barrier. It is rapidly taken up by dopaminergic neurons and converted to dopamine. It is used for the treatment of parkinsonism and is usually given with agents that inhibit its conversion to dopamine outside of the central nervous system. [NIH]

**Library Services:** Services offered to the library user. They include reference and circulation. [NIH]

**Life Expectancy:** A figure representing the number of years, based on known statistics, to which any person of a given age may reasonably expect to live. [NIH]

**Ligament:** A band of fibrous tissue that connects bones or cartilages, serving to support and strengthen joints. [EU]

**Ligands:** A RNA simulation method developed by the MIT. [NIH]

**Linkage:** The tendency of two or more genes in the same chromosome to remain together from one generation to the next more frequently than expected according to the law of independent assortment. [NIH]

**Linkage Disequilibrium:** Nonrandom association of linked genes. This is the tendency of the alleles of two separate but already linked loci to be found together more frequently than would be expected by chance alone. [NIH]

**Lipase:** An enzyme of the hydrolase class that catalyzes the reaction of triacylglycerol and water to yield diacylglycerol and a fatty acid anion. It is produced by glands on the tongue and by the pancreas and initiates the digestion of dietary fats. (From Dorland, 27th ed) EC 3.1.1.3. [NIH]

**Lipid:** Fat. [NIH]

**Lipid Peroxidation:** Peroxidase catalyzed oxidation of lipids using hydrogen peroxide as an electron acceptor. [NIH]

**Lipomatosis:** A disorder consisting of the accumulation of abnormal localized, or tumor-like fat in the tissues. [NIH]

**Lipopolysaccharides:** Substance consisting of polysaccaride and lipid. [NIH]

**Liver:** A large, glandular organ located in the upper abdomen. The liver cleanses the blood and aids in digestion by secreting bile. [NIH]

**Liver cancer:** A disease in which malignant (cancer) cells are found in the tissues of the liver. [NIH]

**Liver Enzyme Tests:** Blood tests that look at how well the liver and biliary system are working. Also called liver function tests. [NIH]

**Liver Transplantation:** The transference of a part of or an entire liver from one human or animal to another. [NIH]

**Localization:** The process of determining or marking the location or site of a lesion or disease. May also refer to the process of keeping a lesion or disease in a specific location or

site. [NIH]

**Localized:** Cancer which has not metastasized yet. [NIH]

**Longitudinal study:** Also referred to as a "cohort study" or "prospective study"; the analytic method of epidemiologic study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed, or exposed in different degrees, to a factor or factors hypothesized to influence the probability of occurrence of a given disease or other outcome. The main feature of this type of study is to observe large numbers of subjects over an extended time, with comparisons of incidence rates in groups that differ in exposure levels. [NIH]

**Long-Term Care:** Care over an extended period, usually for a chronic condition or disability, requiring periodic, intermittent, or continuous care. [NIH]

**Loop:** A wire usually of platinum bent at one end into a small loop (usually 4 mm inside diameter) and used in transferring microorganisms. [NIH]

**Low Back Pain:** Acute or chronic pain in the lumbar or sacral regions, which may be associated with musculo-ligamentous sprains and strains; intervertebral disk displacement; and other conditions. [NIH]

**Lucida:** An instrument, invented by Wollaton, consisting essentially of a prism or a mirror through which an object can be viewed so as to appear on a plane surface seen in direct view and on which the outline of the object may be traced. [NIH]

**Luciferase:** Any one of several enzymes that catalyze the bioluminescent reaction in certain marine crustaceans, fish, bacteria, and insects. The enzyme is a flavoprotein; it oxidizes luciferins to an electronically excited compound that emits energy in the form of light. The color of light emitted varies with the organism. The firefly enzyme is a valuable reagent for measurement of ATP concentration. (Dorland, 27th ed) EC 1.13.12.-. [NIH]

**Lumbar:** Pertaining to the loins, the part of the back between the thorax and the pelvis. [EU]

**Lupus:** A form of cutaneous tuberculosis. It is seen predominantly in women and typically involves the nasal, buccal, and conjunctival mucosa. [NIH]

**Lyme Disease:** An infectious disease caused by a spirochete, Borrelia burgdorferi, which is transmitted chiefly by Ixodes dammini and pacificus ticks in the United States and Ixodes ricinis in Europe. It is a disease with early and late cutaneous manifestations plus involvement of the nervous system, heart, eye, and joints in variable combinations. The disease was formerly known as Lyme arthritis and first discovered at Old Lyme, Connecticut. [NIH]

**Lymph:** The almost colorless fluid that travels through the lymphatic system and carries cells that help fight infection and disease. [NIH]

**Lymph node:** A rounded mass of lymphatic tissue that is surrounded by a capsule of connective tissue. Also known as a lymph gland. Lymph nodes are spread out along lymphatic vessels and contain many lymphocytes, which filter the lymphatic fluid (lymph). [NIH]

**Lymphatic:** The tissues and organs, including the bone marrow, spleen, thymus, and lymph nodes, that produce and store cells that fight infection and disease. [NIH]

**Lymphatic system:** The tissues and organs that produce, store, and carry white blood cells that fight infection and other diseases. This system includes the bone marrow, spleen, thymus, lymph nodes and a network of thin tubes that carry lymph and white blood cells. These tubes branch, like blood vessels, into all the tissues of the body. [NIH]

**Lymphocyte:** A white blood cell. Lymphocytes have a number of roles in the immune system, including the production of antibodies and other substances that fight infection and

diseases. [NIH]

**Lymphocytic:** Referring to lymphocytes, a type of white blood cell. [NIH]

**Lymphoid:** Referring to lymphocytes, a type of white blood cell. Also refers to tissue in which lymphocytes develop. [NIH]

**Lymphoma:** A general term for various neoplastic diseases of the lymphoid tissue. [NIH]

**Lytic:** 1. Pertaining to lysis or to a lysin. 2. Producing lysis. [EU]

**Magnetic Resonance Imaging:** Non-invasive method of demonstrating internal anatomy based on the principle that atomic nuclei in a strong magnetic field absorb pulses of radiofrequency energy and emit them as radiowaves which can be reconstructed into computerized images. The concept includes proton spin tomographic techniques. [NIH]

**Malabsorption:** Impaired intestinal absorption of nutrients. [EU]

**Malignant:** Cancerous; a growth with a tendency to invade and destroy nearby tissue and spread to other parts of the body. [NIH]

**Malignant tumor:** A tumor capable of metastasizing. [NIH]

**Malnutrition:** A condition caused by not eating enough food or not eating a balanced diet. [NIH]

**Mammary:** Pertaining to the mamma, or breast. [EU]

**Mania:** Excitement of psychotic proportions manifested by mental and physical hyperactivity, disorganization of behaviour, and elevation of mood. [EU]

**Manic:** Affected with mania. [EU]

**Manic-depressive psychosis:** One of a group of psychotic reactions, fundamentally marked by severe mood swings and a tendency to remission and recurrence. [NIH]

**Manifest:** Being the part or aspect of a phenomenon that is directly observable : concretely expressed in behaviour. [EU]

**Mechanoreceptors:** Cells specialized to transduce mechanical stimuli and relay that information centrally in the nervous system. Mechanoreceptors include hair cells, which mediate hearing and balance, and the various somatosensory receptors, often with non-neural accessory structures. [NIH]

**Median Nerve:** A major nerve of the upper extremity. In humans, the fibers of the median nerve originate in the lower cervical and upper thoracic spinal cord (usually C6 to T1), travel via the brachial plexus, and supply sensory and motor innervation to parts of the forearm and hand. [NIH]

**Mediate:** Indirect; accomplished by the aid of an intervening medium. [EU]

**Mediator:** An object or substance by which something is mediated, such as (1) a structure of the nervous system that transmits impulses eliciting a specific response; (2) a chemical substance (transmitter substance) that induces activity in an excitable tissue, such as nerve or muscle; or (3) a substance released from cells as the result of the interaction of antigen with antibody or by the action of antigen with a sensitized lymphocyte. [EU]

**Medicament:** A medicinal substance or agent. [EU]

**MEDLINE:** An online database of MEDLARS, the computerized bibliographic Medical Literature Analysis and Retrieval System of the National Library of Medicine. [NIH]

**Megaloblastic:** A large abnormal red blood cell appearing in the blood in pernicious anaemia. [EU]

**Melanin:** The substance that gives the skin its color. [NIH]

**Melanocytes:** Epidermal dendritic pigment cells which control long-term morphological color changes by alteration in their number or in the amount of pigment they produce and store in the pigment containing organelles called melanosomes. Melanophores are larger cells which do not exist in mammals. [NIH]

**Melanoma:** A form of skin cancer that arises in melanocytes, the cells that produce pigment. Melanoma usually begins in a mole. [NIH]

**Memantine:** Amantadine derivative that has some dopaminergic effects. It has been proposed as an antiparkinson agent. [NIH]

**Membrane:** A very thin layer of tissue that covers a surface. [NIH]

**Membrane Glycoproteins:** Glycoproteins found on the membrane or surface of cells. [NIH]

**Membrane Proteins:** Proteins which are found in membranes including cellular and intracellular membranes. They consist of two types, peripheral and integral proteins. They include most membrane-associated enzymes, antigenic proteins, transport proteins, and drug, hormone, and lectin receptors. [NIH]

**Memory:** Complex mental function having four distinct phases: (1) memorizing or learning, (2) retention, (3) recall, and (4) recognition. Clinically, it is usually subdivided into immediate, recent, and remote memory. [NIH]

**Meninges:** The three membranes that cover and protect the brain and spinal cord. [NIH]

**Meningitis:** Inflammation of the meninges. When it affects the dura mater, the disease is termed pachymeningitis; when the arachnoid and pia mater are involved, it is called leptomeningitis, or meningitis proper. [EU]

**Mental:** Pertaining to the mind; psychic. 2. (L. mentum chin) pertaining to the chin. [EU]

**Mental Disorders:** Psychiatric illness or diseases manifested by breakdowns in the adaptational process expressed primarily as abnormalities of thought, feeling, and behavior producing either distress or impairment of function. [NIH]

**Mental Health:** The state wherein the person is well adjusted. [NIH]

**Mental Retardation:** Refers to sub-average general intellectual functioning which originated during the developmental period and is associated with impairment in adaptive behavior. [NIH]

**Mercury:** A silver metallic element that exists as a liquid at room temperature. It has the atomic symbol Hg (from hydrargyrum, liquid silver), atomic number 80, and atomic weight 200.59. Mercury is used in many industrial applications and its salts have been employed therapeutically as purgatives, antisyphilitics, disinfectants, and astringents. It can be absorbed through the skin and mucous membranes which leads to mercury poisoning. Because of its toxicity, the clinical use of mercury and mercurials is diminishing. [NIH]

**Mesna:** A sulfhydryl compound used to prevent urothelial toxicity by inactivating metabolites from antineoplastic agents, such as ifosfamide or cyclophosphamide. [NIH]

**Meta-Analysis:** A quantitative method of combining the results of independent studies (usually drawn from the published literature) and synthesizing summaries and conclusions which may be used to evaluate therapeutic effectiveness, plan new studies, etc., with application chiefly in the areas of research and medicine. [NIH]

**Metabolic disorder:** A condition in which normal metabolic processes are disrupted, usually because of a missing enzyme. [NIH]

**Metabolite:** Any substance produced by metabolism or by a metabolic process. [EU]

**Metastasis:** The spread of cancer from one part of the body to another. Tumors formed from cells that have spread are called "secondary tumors" and contain cells that are like those in

the original (primary) tumor. The plural is metastases. [NIH]

**Metastatic:** Having to do with metastasis, which is the spread of cancer from one part of the body to another. [NIH]

**Methionine:** A sulfur containing essential amino acid that is important in many body functions. It is a chelating agent for heavy metals. [NIH]

**Metronidazole:** Antiprotozoal used in amebiasis, trichomoniasis, giardiasis, and as treponemacide in livestock. It has also been proposed as a radiation sensitizer for hypoxic cells. According to the Fourth Annual Report on Carcinogens (NTP 85-002, 1985, p133), this substance may reasonably be anticipated to be a carcinogen (Merck, 11th ed). [NIH]

**MI:** Myocardial infarction. Gross necrosis of the myocardium as a result of interruption of the blood supply to the area; it is almost always caused by atherosclerosis of the coronary arteries, upon which coronary thrombosis is usually superimposed. [NIH]

**Microbe:** An organism which cannot be observed with the naked eye; e. g. unicellular animals, lower algae, lower fungi, bacteria. [NIH]

**Microbiology:** The study of microorganisms such as fungi, bacteria, algae, archaea, and viruses. [NIH]

**Microcirculation:** The vascular network lying between the arterioles and venules; includes capillaries, metarterioles and arteriovenous anastomoses. Also, the flow of blood through this network. [NIH]

**Microglia:** The third type of glial cell, along with astrocytes and oligodendrocytes (which together form the macroglia). Microglia vary in appearance depending on developmental stage, functional state, and anatomical location; subtype terms include ramified, perivascular, ameboid, resting, and activated. Microglia clearly are capable of phagocytosis and play an important role in a wide spectrum of neuropathologies. They have also been suggested to act in several other roles including in secretion (e.g., of cytokines and neural growth factors), in immunological processing (e.g., antigen presentation), and in central nervous system development and remodeling. [NIH]

**Microorganism:** An organism that can be seen only through a microscope. Microorganisms include bacteria, protozoa, algae, and fungi. Although viruses are not considered living organisms, they are sometimes classified as microorganisms. [NIH]

**Micro-organism:** An organism which cannot be observed with the naked eye; e. g. unicellular animals, lower algae, lower fungi, bacteria. [NIH]

**Microscopy:** The application of microscope magnification to the study of materials that cannot be properly seen by the unaided eye. [NIH]

**Microspheres:** Small uniformly-sized spherical particles frequently labeled with radioisotopes or various reagents acting as tags or markers. [NIH]

**Microtubule-Associated Proteins:** High molecular weight proteins found in the microtubules of the cytoskeletal system. Under certain conditions they are required for tubulin assembly into the microtubules and stabilize the assembled microtubules. [NIH]

**Microtubules:** Slender, cylindrical filaments found in the cytoskeleton of plant and animal cells. They are composed of the protein tubulin. [NIH]

**Milliliter:** A measure of volume for a liquid. A milliliter is approximately 950-times smaller than a quart and 30-times smaller than a fluid ounce. A milliliter of liquid and a cubic centimeter (cc) of liquid are the same. [NIH]

**Mitochondria:** Parts of a cell where aerobic production (also known as cell respiration) takes place. [NIH]

**Mitosis:** A method of indirect cell division by means of which the two daughter nuclei normally receive identical complements of the number of chromosomes of the somatic cells of the species. [NIH]

**Mitotic:** Cell resulting from mitosis. [NIH]

**Mitral Valve:** The valve between the left atrium and left ventricle of the heart. [NIH]

**Mobility:** Capability of movement, of being moved, or of flowing freely. [EU]

**Mobilization:** The process of making a fixed part or stored substance mobile, as by separating a part from surrounding structures to make it accessible for an operative procedure or by causing release into the circulation for body use of a substance stored in the body. [EU]

**Modeling:** A treatment procedure whereby the therapist presents the target behavior which the learner is to imitate and make part of his repertoire. [NIH]

**Modification:** A change in an organism, or in a process in an organism, that is acquired from its own activity or environment. [NIH]

**Molecular:** Of, pertaining to, or composed of molecules : a very small mass of matter. [EU]

**Molecular Structure:** The location of the atoms, groups or ions relative to one another in a molecule, as well as the number, type and location of covalent bonds. [NIH]

**Molecule:** A chemical made up of two or more atoms. The atoms in a molecule can be the same (an oxygen molecule has two oxygen atoms) or different (a water molecule has two hydrogen atoms and one oxygen atom). Biological molecules, such as proteins and DNA, can be made up of many thousands of atoms. [NIH]

**Monitor:** An apparatus which automatically records such physiological signs as respiration, pulse, and blood pressure in an anesthetized patient or one undergoing surgical or other procedures. [NIH]

**Monoamine:** Enzyme that breaks down dopamine in the astrocytes and microglia. [NIH]

**Monoamine Oxidase:** An enzyme that catalyzes the oxidative deamination of naturally occurring monoamines. It is a flavin-containing enzyme that is localized in mitochondrial membranes, whether in nerve terminals, the liver, or other organs. Monoamine oxidase is important in regulating the metabolic degradation of catecholamines and serotonin in neural or target tissues. Hepatic monoamine oxidase has a crucial defensive role in inactivating circulating monoamines or those, such as tyramine, that originate in the gut and are absorbed into the portal circulation. (From Goodman and Gilman's, The Pharmacological Basis of Therapeutics, 8th ed, p415) EC 1.4.3.4. [NIH]

**Monoclonal:** An antibody produced by culturing a single type of cell. It therefore consists of a single species of immunoglobulin molecules. [NIH]

**Monocytes:** Large, phagocytic mononuclear leukocytes produced in the vertebrate bone marrow and released into the blood; contain a large, oval or somewhat indented nucleus surrounded by voluminous cytoplasm and numerous organelles. [NIH]

**Mononeuropathies:** Disease or trauma involving a single peripheral nerve in isolation, or out of proportion to evidence of diffuse peripheral nerve dysfunction. Mononeuropathy multiplex refers to a condition characterized by multiple isolated nerve injuries. Mononeuropathies may result from a wide variety of causes, includingischemia; traumatic injury; compression; connective tissue diseases; cumulative trauma disorders; and other conditions. [NIH]

**Mononuclear:** A cell with one nucleus. [NIH]

**Monophosphate:** So called second messenger for neurotransmitters and hormones. [NIH]

**Mood Disorders:** Those disorders that have a disturbance in mood as their predominant feature. [NIH]

**Morphine:** The principal alkaloid in opium and the prototype opiate analgesic and narcotic. Morphine has widespread effects in the central nervous system and on smooth muscle. [NIH]

**Morphological:** Relating to the configuration or the structure of live organs. [NIH]

**Morphology:** The science of the form and structure of organisms (plants, animals, and other forms of life). [NIH]

**Motility:** The ability to move spontaneously. [EU]

**Motor nerve:** An efferent nerve conveying an impulse that excites muscular contraction. [NIH]

**Motor Neurons:** Neurons which activate muscle cells. [NIH]

**Movement Disorders:** Syndromes which feature dyskinesias as a cardinal manifestation of the disease process. Included in this category are degenerative, hereditary, post-infectious, medication-induced, post-inflammatory, and post-traumatic conditions. [NIH]

**Mucinous:** Containing or resembling mucin, the main compound in mucus. [NIH]

**Mucosa:** A mucous membrane, or tunica mucosa. [EU]

**Mucositis:** A complication of some cancer therapies in which the lining of the digestive system becomes inflamed. Often seen as sores in the mouth. [NIH]

**Multiple Myeloma:** A malignant tumor of plasma cells usually arising in the bone marrow; characterized by diffuse involvement of the skeletal system, hyperglobulinemia, Bence-Jones proteinuria, and anemia. [NIH]

**Multiple sclerosis:** A disorder of the central nervous system marked by weakness, numbness, a loss of muscle coordination, and problems with vision, speech, and bladder control. Multiple sclerosis is thought to be an autoimmune disease in which the body's immune system destroys myelin. Myelin is a substance that contains both protein and fat (lipid) and serves as a nerve insulator and helps in the transmission of nerve signals. [NIH]

**Muscle Fibers:** Large single cells, either cylindrical or prismatic in shape, that form the basic unit of muscle tissue. They consist of a soft contractile substance enclosed in a tubular sheath. [NIH]

**Muscle Hypertonia:** Abnormal increase in skeletal or smooth muscle tone. Skeletal muscle hypertonicity may be associated with pyramidal tract lesions or basal ganglia diseases. [NIH]

**Muscle relaxant:** An agent that specifically aids in reducing muscle tension, as those acting at the polysynaptic neurons of motor nerves (e.g. meprobamate) or at the myoneural junction (curare and related compounds). [EU]

**Muscle Spindles:** Mechanoreceptors found between skeletal muscle fibers. Muscle spindles are arranged in parallel with muscle fibers and respond to the passive stretch of the muscle, but cease to discharge if the muscle contracts isotonically, thus signaling muscle length. The muscle spindles are the receptors responsible for the stretch or myotactic reflex. [NIH]

**Muscular Atrophy:** Derangement in size and number of muscle fibers occurring with aging, reduction in blood supply, or following immobilization, prolonged weightlessness, malnutrition, and particularly in denervation. [NIH]

**Muscular Diseases:** Acquired, familial, and congenital disorders of skeletal muscle and smooth muscle. [NIH]

**Muscular Dystrophies:** A general term for a group of inherited disorders which are characterized by progressive degeneration of skeletal muscles. [NIH]

**Mutagenic:** Inducing genetic mutation. [EU]

**Mycosis:** Any disease caused by a fungus. [EU]

**Mycosis Fungoides:** A chronic malignant T-cell lymphoma of the skin. In the late stages the lymph nodes and viscera are affected. [NIH]

**Myelin:** The fatty substance that covers and protects nerves. [NIH]

**Myelin Proteins:** Proteins found in the myelin sheath. The major proteins of central nervous system myelin include: myelin proteolipid protein, myelin basic proteins, and myelin-associated glycoprotein. The major proteins of peripheral nervous system myelin include: myelin basic proteins (myelin p1 protein and myelin p2 protein), myelin p0 protein, and myelin-associated glycoprotein. [NIH]

**Myelin Sheath:** The lipid-rich sheath investing many axons in both the central and peripheral nervous systems. The myelin sheath is an electrical insulator and allows faster and more energetically efficient conduction of impulses. The sheath is formed by the cell membranes of glial cells (Schwann cells in the peripheral and oligodendroglia in the central nervous system). Deterioration of the sheath in demyelinating diseases is a serious clinical problem. [NIH]

**Myelitis:** Inflammation of the spinal cord. Relatively common etiologies include infections; autoimmune diseases; spinal cord; and ischemia (see also spinal cord vascular diseases). Clinical features generally include weakness, sensory loss, localized pain, incontinence, and other signs of autonomic dysfunction. [NIH]

**Myelofibrosis:** A disorder in which the bone marrow is replaced by fibrous tissue. [NIH]

**Myeloma:** Cancer that arises in plasma cells, a type of white blood cell. [NIH]

**Myocarditis:** Inflammation of the myocardium; inflammation of the muscular walls of the heart. [EU]

**Myocardium:** The muscle tissue of the heart composed of striated, involuntary muscle known as cardiac muscle. [NIH]

**Myoclonus:** Involuntary shock-like contractions, irregular in rhythm and amplitude, followed by relaxation, of a muscle or a group of muscles. This condition may be a feature of some central nervous systems diseases (e.g., epilepsy, myoclonic). Nocturnal myoclonus may represent a normal physiologic event or occur as the principal feature of the nocturnal myoclonus syndrome. (From Adams et al., Principles of Neurology, 6th ed, pp102-3). [NIH]

**Myofibrils:** Highly organized bundles of actin, myosin, and other proteins in the cytoplasm of skeletal and cardiac muscle cells that contract by a sliding filament mechanism. [NIH]

**Myopathy:** Any disease of a muscle. [EU]

**Myopia:** That error of refraction in which rays of light entering the eye parallel to the optic axis are brought to a focus in front of the retina, as a result of the eyeball being too long from front to back (axial m.) or of an increased strength in refractive power of the media of the eye (index m.). Called also nearsightedness, because the near point is less distant than it is in emmetropia with an equal amplitude of accommodation. [EU]

**Myotonic Dystrophy:** A condition presenting muscle weakness and wasting which may be progressive. [NIH]

**Naive:** Used to describe an individual who has never taken a certain drug or class of drugs (e. g., AZT-naive, antiretroviral-naive), or to refer to an undifferentiated immune system cell. [NIH]

**Narcosis:** A general and nonspecific reversible depression of neuronal excitability, produced by a number of physical and chemical aspects, usually resulting in stupor. [NIH]

**Narcotic:** 1. Pertaining to or producing narcosis. 2. An agent that produces insensibility or stupor, applied especially to the opioids, i.e. to any natural or synthetic drug that has morphine-like actions. [EU]

**Nausea:** An unpleasant sensation in the stomach usually accompanied by the urge to vomit. Common causes are early pregnancy, sea and motion sickness, emotional stress, intense pain, food poisoning, and various enteroviruses. [NIH]

**NCI:** National Cancer Institute. NCI, part of the National Institutes of Health of the United States Department of Health and Human Services, is the federal government's principal agency for cancer research. NCI conducts, coordinates, and funds cancer research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer. Access the NCI Web site at http://cancer.gov. [NIH]

**Nearsightedness:** The common term for myopia. [NIH]

**Need:** A state of tension or dissatisfaction felt by an individual that impels him to action toward a goal he believes will satisfy the impulse. [NIH]

**Neocortex:** The largest portion of the cerebral cortex. It is composed of neurons arranged in six layers. [NIH]

**Neoplasia:** Abnormal and uncontrolled cell growth. [NIH]

**Neoplasm:** A new growth of benign or malignant tissue. [NIH]

**Neoplastic:** Pertaining to or like a neoplasm (= any new and abnormal growth); pertaining to neoplasia (= the formation of a neoplasm). [EU]

**Nephropathy:** Disease of the kidneys. [EU]

**Nerve:** A cordlike structure of nervous tissue that connects parts of the nervous system with other tissues of the body and conveys nervous impulses to, or away from, these tissues. [NIH]

**Nerve Fibers:** Slender processes of neurons, especially the prolonged axons that conduct nerve impulses. [NIH]

**Nerve Growth Factor:** Nerve growth factor is the first of a series of neurotrophic factors that were found to influence the growth and differentiation of sympathetic and sensory neurons. It is comprised of alpha, beta, and gamma subunits. The beta subunit is responsible for its growth stimulating activity. [NIH]

**Nerve Regeneration:** Renewal or physiological repair of damaged nerve tissue. [NIH]

**Nervous System:** The entire nerve apparatus composed of the brain, spinal cord, nerves and ganglia. [NIH]

**Neural:** 1. Pertaining to a nerve or to the nerves. 2. Situated in the region of the spinal axis, as the neutral arch. [EU]

**Neuralgia:** Intense or aching pain that occurs along the course or distribution of a peripheral or cranial nerve. [NIH]

**Neuritis:** A general term indicating inflammation of a peripheral or cranial nerve. Clinical manifestation may include pain; paresthesias; paresis; or hypesthesia. [NIH]

**Neurodegenerative Diseases:** Hereditary and sporadic conditions which are characterized by progressive nervous system dysfunction. These disorders are often associated with atrophy of the affected central or peripheral nervous system structures. [NIH]

**Neurofibrillary Tangles:** Abnormal structures located in various parts of the brain and composed of dense arrays of paired helical filaments (neurofilaments and microtubules). These double helical stacks of transverse subunits are twisted into left-handed ribbon-like filaments that likely incorporate the following proteins: (1) the intermediate filaments: medium- and high-molecular-weight neurofilaments; (2) the microtubule-associated

proteins map-2 and tau; (3) actin; and (4) ubiquitin. As one of the hallmarks of Alzheimer disease, the neurofibrillary tangles eventually occupy the whole of the cytoplasm in certain classes of cell in the neocortex, hippocampus, brain stem, and diencephalon. The number of these tangles, as seen in post mortem histology, correlates with the degree of dementia during life. Some studies suggest that tangle antigens leak into the systemic circulation both in the course of normal aging and in cases of Alzheimer disease. [NIH]

**Neurofilaments:** Bundle of neuronal fibers. [NIH]

**Neurologic:** Having to do with nerves or the nervous system. [NIH]

**Neuromuscular:** Pertaining to muscles and nerves. [EU]

**Neuromuscular Diseases:** A general term encompassing lower motor neuron disease; peripheral nervous system diseases; and certain muscular diseases. Manifestations include muscle weakness; fasciculation; muscle atrophy; spasm; myokymia; muscle hypertonia, myalgias, and musclehypotonia. [NIH]

**Neuromuscular Junction:** The synapse between a neuron and a muscle. [NIH]

**Neuronal:** Pertaining to a neuron or neurons (= conducting cells of the nervous system). [EU]

**Neurons:** The basic cellular units of nervous tissue. Each neuron consists of a body, an axon, and dendrites. Their purpose is to receive, conduct, and transmit impulses in the nervous system. [NIH]

**Neuropathy:** A problem in any part of the nervous system except the brain and spinal cord. Neuropathies can be caused by infection, toxic substances, or disease. [NIH]

**Neuropeptide:** A member of a class of protein-like molecules made in the brain. Neuropeptides consist of short chains of amino acids, with some functioning as neurotransmitters and some functioning as hormones. [NIH]

**Neurophysiology:** The scientific discipline concerned with the physiology of the nervous system. [NIH]

**Neurotoxic:** Poisonous or destructive to nerve tissue. [EU]

**Neurotoxicity:** The tendency of some treatments to cause damage to the nervous system. [NIH]

**Neurotoxin:** A substance that is poisonous to nerve tissue. [NIH]

**Neurotransmitter:** Any of a group of substances that are released on excitation from the axon terminal of a presynaptic neuron of the central or peripheral nervous system and travel across the synaptic cleft to either excite or inhibit the target cell. Among the many substances that have the properties of a neurotransmitter are acetylcholine, norepinephrine, epinephrine, dopamine, glycine, y-aminobutyrate, glutamic acid, substance P, enkephalins, endorphins, and serotonin. [EU]

**Neurotrophins:** A nerve growth factor. [NIH]

**Neutrophil:** A type of white blood cell. [NIH]

**Niacin:** Water-soluble vitamin of the B complex occurring in various animal and plant tissues. Required by the body for the formation of coenzymes NAD and NADP. Has pellagra-curative, vasodilating, and antilipemic properties. [NIH]

**Nicotine:** Nicotine is highly toxic alkaloid. It is the prototypical agonist at nicotinic cholinergic receptors where it dramatically stimulates neurons and ultimately blocks synaptic transmission. Nicotine is also important medically because of its presence in tobacco smoke. [NIH]

**Nimodipine:** A calcium channel blockader with preferential cerebrovascular activity. It has marked cerebrovascular dilating effects and lowers blood pressure. [NIH]

**Nitrogen:** An element with the atomic symbol N, atomic number 7, and atomic weight 14. Nitrogen exists as a diatomic gas and makes up about 78% of the earth's atmosphere by volume. It is a constituent of proteins and nucleic acids and found in all living cells. [NIH]

**Nitrous Oxide:** Nitrogen oxide (N2O). A colorless, odorless gas that is used as an anesthetic and analgesic. High concentrations cause a narcotic effect and may replace oxygen, causing death by asphyxia. It is also used as a food aerosol in the preparation of whipping cream. [NIH]

**Nonmalignant:** Not cancerous. [NIH]

**Norepinephrine:** Precursor of epinephrine that is secreted by the adrenal medulla and is a widespread central and autonomic neurotransmitter. Norepinephrine is the principal transmitter of most postganglionic sympathetic fibers and of the diffuse projection system in the brain arising from the locus ceruleus. It is also found in plants and is used pharmacologically as a sympathomimetic. [NIH]

**Nuclear:** A test of the structure, blood flow, and function of the kidneys. The doctor injects a mildly radioactive solution into an arm vein and uses x-rays to monitor its progress through the kidneys. [NIH]

**Nuclear Envelope:** The membrane system of the cell nucleus that surrounds the nucleoplasm. It consists of two concentric membranes separated by the perinuclear space. The structures of the envelope where it opens to the cytoplasm are called the nuclear pores (nuclear pore). [NIH]

**Nuclear Medicine:** A specialty field of radiology concerned with diagnostic, therapeutic, and investigative use of radioactive compounds in a pharmaceutical form. [NIH]

**Nuclear Pore:** An opening through the nuclear envelope formed by the nuclear pore complex which transports nuclear proteins or RNA into or out of the cell nucleus and which, under some conditions, acts as an ion channel. [NIH]

**Nuclei:** A body of specialized protoplasm found in nearly all cells and containing the chromosomes. [NIH]

**Nucleic acid:** Either of two types of macromolecule (DNA or RNA) formed by polymerization of nucleotides. Nucleic acids are found in all living cells and contain the information (genetic code) for the transfer of genetic information from one generation to the next. [NIH]

**Nucleus:** A body of specialized protoplasm found in nearly all cells and containing the chromosomes. [NIH]

**Nutritional Status:** State of the body in relation to the consumption and utilization of nutrients. [NIH]

**Nystagmus:** Rhythmical oscillation of the eyeballs, either pendular or jerky. [NIH]

**Obsessive-Compulsive Disorder:** An anxiety disorder characterized by recurrent, persistent obsessions or compulsions. Obsessions are the intrusive ideas, thoughts, or images that are experienced as senseless or repugnant. Compulsions are repetitive and seemingly purposeful behavior which the individual generally recognizes as senseless and from which the individual does not derive pleasure although it may provide a release from tension. [NIH]

**Occupational Exposure:** The exposure to potentially harmful chemical, physical, or biological agents that occurs as a result of one's occupation. [NIH]

**Ointments:** Semisolid preparations used topically for protective emollient effects or as a vehicle for local administration of medications. Ointment bases are various mixtures of fats, waxes, animal and plant oils and solid and liquid hydrocarbons. [NIH]

**Oligodendroglia:** A class of neuroglial (macroglial) cells in the central nervous system.

Oligodendroglia may be called interfascicular, perivascular, or perineuronal satellite cells according to their location. The most important recognized function of these cells is the formation of the insulating myelin sheaths of axons in the central nervous system. [NIH]

**Oliguria:** Clinical manifestation of the urinary system consisting of a decrease in the amount of urine secreted. [NIH]

**Oncogene:** A gene that normally directs cell growth. If altered, an oncogene can promote or allow the uncontrolled growth of cancer. Alterations can be inherited or caused by an environmental exposure to carcinogens. [NIH]

**Oncogenic:** Chemical, viral, radioactive or other agent that causes cancer; carcinogenic. [NIH]

**Oncolysis:** The destruction of or disposal by absorption of any neoplastic cells. [NIH]

**Oncolytic:** Pertaining to, characterized by, or causing oncolysis (= the lysis or destruction of tumour cells). [EU]

**Oocytes:** Female germ cells in stages between the prophase of the first maturation division and the completion of the second maturation division. [NIH]

**Opacity:** Degree of density (area most dense taken for reading). [NIH]

**Open Reading Frames:** Reading frames where successive nucleotide triplets can be read as codons specifying amino acids and where the sequence of these triplets is not interrupted by stop codons. [NIH]

**Opiate:** A remedy containing or derived from opium; also any drug that induces sleep. [EU]

**Opioid Peptides:** The endogenous peptides with opiate-like activity. The three major classes currently recognized are the enkephalins, the dynorphins, and the endorphins. Each of these families derives from different precursors, proenkephalin, prodynorphin, and pro-opiomelanocortin, respectively. There are also at least three classes of opioid receptors, but the peptide families do not map to the receptors in a simple way. [NIH]

**Opium:** The air-dried exudate from the unripe seed capsule of the opium poppy, Papaver somniferum, or its variant, P. album. It contains a number of alkaloids, but only a few - morphine, codeine, and papaverine - have clinical significance. Opium has been used as an analgesic, antitussive, antidiarrheal, and antispasmodic. [NIH]

**Opportunistic Infections:** An infection caused by an organism which becomes pathogenic under certain conditions, e.g., during immunosuppression. [NIH]

**Opsin:** A protein formed, together with retinene, by the chemical breakdown of meta-rhodopsin. [NIH]

**Optic Atrophy:** Atrophy of the optic disk which may be congenital or acquired. This condition indicates a deficiency in the number of nerve fibers which arise in the retina and converge to form the optic disk, optic nerve, optic chiasm, and optic tracts. Glaucoma, ischemia, inflammation, a chronic elevation of intracranial pressure, toxins, optic nerve compression, and inherited conditions are relatively common causes of this condition. [NIH]

**Optic Chiasm:** The X-shaped structure formed by the meeting of the two optic nerves. At the optic chiasm the fibers from the medial part of each retina cross to project to the other side of the brain while the lateral retinal fibers continue on the same side. As a result each half of the brain receives information about the contralateral visual field from both eyes. [NIH]

**Optic disc:** The circular area (disc) where the optic nerve connects to the retina. [NIH]

**Optic Disk:** The portion of the optic nerve seen in the fundus with the ophthalmoscope. It is formed by the meeting of all the retinal ganglion cell axons as they enter the optic nerve. [NIH]

**Optic Nerve:** The 2nd cranial nerve. The optic nerve conveys visual information from the retina to the brain. The nerve carries the axons of the retinal ganglion cells which sort at the optic chiasm and continue via the optic tracts to the brain. The largest projection is to the lateral geniculate nuclei; other important targets include the superior colliculi and the suprachiasmatic nuclei. Though known as the second cranial nerve, it is considered part of the central nervous system. [NIH]

**Optic Nerve Diseases:** Conditions which produce injury or dysfunction of the second cranial or optic nerve, which is generally considered a component of the central nervous system. Damage to optic nerve fibers may occur at or near their origin in the retina, at the optic disk, or in the nerve, optic chiasm, optic tract, or lateral geniculate nuclei. Clinical manifestations may include decreased visual acuity and contrast sensitivity, impaired color vision, and an afferent pupillary defect. [NIH]

**Optic Neuritis:** Inflammation of the optic nerve. Commonly associated conditions include autoimmune disorders such as multiple sclerosis, infections, and granulomatous diseases. Clinical features include retro-orbital pain that is aggravated by eye movement, loss of color vision, and contrast sensitivity that may progress to severe visual loss, an afferent pupillary defect (Marcus-Gunn pupil), and in some instances optic disc hyperemia and swelling. Inflammation may occur in the portion of the nerve within the globe (neuropapillitis or anterior optic neuritis) or the portion behind the globe (retrobulbar neuritis or posterior optic neuritis). [NIH]

**Orbital:** Pertaining to the orbit (= the bony cavity that contains the eyeball). [EU]

**Organ Culture:** The growth in aseptic culture of plant organs such as roots or shoots, beginning with organ primordia or segments and maintaining the characteristics of the organ. [NIH]

**Organelles:** Specific particles of membrane-bound organized living substances present in eukaryotic cells, such as the mitochondria; the golgi apparatus; endoplasmic reticulum; lysomomes; plastids; and vacuoles. [NIH]

**Organophosphorus Compounds:** Organic compounds that contain phosphorus as an integral part of the molecule. [NIH]

**Osteoarthritis:** A progressive, degenerative joint disease, the most common form of arthritis, especially in older persons. The disease is thought to result not from the aging process but from biochemical changes and biomechanical stresses affecting articular cartilage. In the foreign literature it is often called osteoarthrosis deformans. [NIH]

**Osteoclasts:** A large multinuclear cell associated with the absorption and removal of bone. An odontoclast, also called cementoclast, is cytomorphologically the same as an osteoclast and is involved in cementum resorption. [NIH]

**Osteomyelitis:** Inflammation of bone caused by a pyogenic organism. It may remain localized or may spread through the bone to involve the marrow, cortex, cancellous tissue, and periosteum. [EU]

**Osteoporosis:** Reduction of bone mass without alteration in the composition of bone, leading to fractures. Primary osteoporosis can be of two major types: postmenopausal osteoporosis and age-related (or senile) osteoporosis. [NIH]

**Outpatient:** A patient who is not an inmate of a hospital but receives diagnosis or treatment in a clinic or dispensary connected with the hospital. [NIH]

**Overdose:** An accidental or deliberate dose of a medication or street drug that is in excess of what is normally used. [NIH]

**Oxidation:** The act of oxidizing or state of being oxidized. Chemically it consists in the

increase of positive charges on an atom or the loss of negative charges. Most biological oxidations are accomplished by the removal of a pair of hydrogen atoms (dehydrogenation) from a molecule. Such oxidations must be accompanied by reduction of an acceptor molecule. Univalent o. indicates loss of one electron; divalent o., the loss of two electrons. [EU]

**Oxidative metabolism:** A chemical process in which oxygen is used to make energy from carbohydrates (sugars). Also known as aerobic respiration, cell respiration, or aerobic metabolism. [NIH]

**Oxidative Phosphorylation:** Electron transfer through the cytochrome system liberating free energy which is transformed into high-energy phosphate bonds. [NIH]

**Oxidative Stress:** A disturbance in the prooxidant-antioxidant balance in favor of the former, leading to potential damage. Indicators of oxidative stress include damaged DNA bases, protein oxidation products, and lipid peroxidation products (Sies, Oxidative Stress, 1991, pxv-xvi). [NIH]

**Paclitaxel:** Antineoplastic agent isolated from the bark of the Pacific yew tree, Taxus brevifolia. Paclitaxel stabilizes microtubules in their polymerized form and thus mimics the action of the proto-oncogene proteins c-mos. [NIH]

**Palliative:** 1. Affording relief, but not cure. 2. An alleviating medicine. [EU]

**Palsies:** Disease of the peripheral nervous system occurring usually after many years of increased lead absorption. [NIH]

**Pancreas:** A mixed exocrine and endocrine gland situated transversely across the posterior abdominal wall in the epigastric and hypochondriac regions. The endocrine portion is comprised of the Islets of Langerhans, while the exocrine portion is a compound acinar gland that secretes digestive enzymes. [NIH]

**Pancreas Transplant:** A surgical procedure that involves replacing the pancreas of a person who has diabetes with a healthy pancreas that can make insulin. The healthy pancreas comes from a donor who has just died or from a living relative. A person can donate half a pancreas and still live normally. [NIH]

**Pancreas Transplantation:** The transference of a pancreas from one human or animal to another. [NIH]

**Pancreatic:** Having to do with the pancreas. [NIH]

**Pancreatic cancer:** Cancer of the pancreas, a salivary gland of the abdomen. [NIH]

**Papilledema:** Swelling around the optic disk. [NIH]

**Paralysis:** Loss of ability to move all or part of the body. [NIH]

**Paraparesis:** Mild to moderate loss of bilateral lower extremity motor function, which may be a manifestation of spinal cord diseases; peripheral nervous system diseases; muscular diseases; intracranial hypertension; parasagittal brain lesions; and other conditions. [NIH]

**Paraplegia:** Severe or complete loss of motor function in the lower extremities and lower portions of the trunk. This condition is most often associated with spinal cord diseases, although brain diseases; peripheral nervous system diseases; neuromuscular diseases; and muscular diseases may also cause bilateral leg weakness. [NIH]

**Parenteral:** Not through the alimentary canal but rather by injection through some other route, as subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intrasternal, intravenous, etc. [EU]

**Paresthesia:** Subjective cutaneous sensations (e.g., cold, warmth, tingling, pressure, etc.) that are experienced spontaneously in the absence of stimulation. [NIH]

**Parietal:** 1. Of or pertaining to the walls of a cavity. 2. Pertaining to or located near the parietal bone, as the parietal lobe. [EU]

**Parietal Lobe:** Upper central part of the cerebral hemisphere. [NIH]

**Parkinsonism:** A group of neurological disorders characterized by hypokinesia, tremor, and muscular rigidity. [EU]

**Paroxysmal:** Recurring in paroxysms (= spasms or seizures). [EU]

**Patch:** A piece of material used to cover or protect a wound, an injured part, etc.: a patch over the eye. [NIH]

**Pathogen:** Any disease-producing microorganism. [EU]

**Pathogenesis:** The cellular events and reactions that occur in the development of disease. [NIH]

**Pathologic:** 1. Indicative of or caused by a morbid condition. 2. Pertaining to pathology (= branch of medicine that treats the essential nature of the disease, especially the structural and functional changes in tissues and organs of the body caused by the disease). [EU]

**Pathologic Processes:** The abnormal mechanisms and forms involved in the dysfunctions of tissues and organs. [NIH]

**Pathologies:** The study of abnormality, especially the study of diseases. [NIH]

**Pathophysiology:** Altered functions in an individual or an organ due to disease. [NIH]

**Patient Education:** The teaching or training of patients concerning their own health needs. [NIH]

**Pedigree:** A record of one's ancestors, offspring, siblings, and their offspring that may be used to determine the pattern of certain genes or disease inheritance within a family. [NIH]

**Pelvic:** Pertaining to the pelvis. [EU]

**Penicillin:** An antibiotic drug used to treat infection. [NIH]

**Pentoxifylline:** A methylxanthine derivative that inhibits phosphodiesterase and affects blood rheology. It improves blood flow by increasing erythrocyte and leukocyte flexibility. It also inhibits platelet aggregation. Pentoxifylline modulates immunologic activity by stimulating cytokine production. [NIH]

**Peptide:** Any compound consisting of two or more amino acids, the building blocks of proteins. Peptides are combined to make proteins. [NIH]

**Perception:** The ability quickly and accurately to recognize similarities and differences among presented objects, whether these be pairs of words, pairs of number series, or multiple sets of these or other symbols such as geometric figures. [NIH]

**Percutaneous:** Performed through the skin, as injection of radiopacque material in radiological examination, or the removal of tissue for biopsy accomplished by a needle. [EU]

**Performance status:** A measure of how well a patient is able to perform ordinary tasks and carry out daily activities. [NIH]

**Perfusion:** Bathing an organ or tissue with a fluid. In regional perfusion, a specific area of the body (usually an arm or a leg) receives high doses of anticancer drugs through a blood vessel. Such a procedure is performed to treat cancer that has not spread. [NIH]

**Pericardium:** The fibroserous sac surrounding the heart and the roots of the great vessels. [NIH]

**Periodontal disease:** Disease involving the supporting structures of the teeth (as the gums and periodontal membranes). [NIH]

**Periodontal disease:** Disease involving the supporting structures of the teeth (as the gums

and periodontal membranes). [NIH]

**Peripheral blood:** Blood circulating throughout the body. [NIH]

**Peripheral Nervous System:** The nervous system outside of the brain and spinal cord. The peripheral nervous system has autonomic and somatic divisions. The autonomic nervous system includes the enteric, parasympathetic, and sympathetic subdivisions. The somatic nervous system includes the cranial and spinal nerves and their ganglia and the peripheral sensory receptors. [NIH]

**Peripheral Nervous System Diseases:** Diseases of the peripheral nerves external to the brain and spinal cord, which includes diseases of the nerve roots, ganglia, plexi, autonomic nerves, sensory nerves, and motor nerves. [NIH]

**Peripheral Neuropathy:** Nerve damage, usually affecting the feet and legs; causing pain, numbness, or a tingling feeling. Also called "somatic neuropathy" or "distal sensory polyneuropathy." [NIH]

**Peripheral Vascular Disease:** Disease in the large blood vessels of the arms, legs, and feet. People who have had diabetes for a long time may get this because major blood vessels in their arms, legs, and feet are blocked and these limbs do not receive enough blood. The signs of PVD are aching pains in the arms, legs, and feet (especially when walking) and foot sores that heal slowly. Although people with diabetes cannot always avoid PVD, doctors say they have a better chance of avoiding it if they take good care of their feet, do not smoke, and keep both their blood pressure and diabetes under good control. [NIH]

**Peritoneal:** Having to do with the peritoneum (the tissue that lines the abdominal wall and covers most of the organs in the abdomen). [NIH]

**Peritoneal Cavity:** The space enclosed by the peritoneum. It is divided into two portions, the greater sac and the lesser sac or omental bursa, which lies behind the stomach. The two sacs are connected by the foramen of Winslow, or epiploic foramen. [NIH]

**Peritoneal Dialysis:** Dialysis fluid being introduced into and removed from the peritoneal cavity as either a continuous or an intermittent procedure. [NIH]

**Peritoneum:** Endothelial lining of the abdominal cavity, the parietal peritoneum covering the inside of the abdominal wall and the visceral peritoneum covering the bowel, the mesentery, and certain of the organs. The portion that covers the bowel becomes the serosal layer of the bowel wall. [NIH]

**Pernicious:** Tending to a fatal issue. [EU]

**Pernicious anemia:** A type of anemia (low red blood cell count) caused by the body's inability to absorb vitamin B12. [NIH]

**Peroneal Nerve:** The lateral of the two terminal branches of the sciatic nerve. The peroneal (or fibular) nerve provides motor and sensory innervation to parts of the leg and foot. [NIH]

**Pesticides:** Chemicals used to destroy pests of any sort. The concept includes fungicides (industrial fungicides), insecticides, rodenticides, etc. [NIH]

**PH:** The symbol relating the hydrogen ion (H+) concentration or activity of a solution to that of a given standard solution. Numerically the pH is approximately equal to the negative logarithm of H+ concentration expressed in molarity. pH 7 is neutral; above it alkalinity increases and below it acidity increases. [EU]

**Pharmaceutical Solutions:** Homogeneous liquid preparations that contain one or more chemical substances dissolved, i.e., molecularly dispersed, in a suitable solvent or mixture of mutually miscible solvents. For reasons of their ingredients, method of preparation, or use, they do not fall into another group of products. [NIH]

**Pharmacokinetic:** The mathematical analysis of the time courses of absorption, distribution, and elimination of drugs. [NIH]

**Pharmacologic:** Pertaining to pharmacology or to the properties and reactions of drugs. [EU]

**Phenotype:** The outward appearance of the individual. It is the product of interactions between genes and between the genotype and the environment. This includes the killer phenotype, characteristic of yeasts. [NIH]

**Phenylalanine:** An aromatic amino acid that is essential in the animal diet. It is a precursor of melanin, dopamine, noradrenalin, and thyroxine. [NIH]

**Phenytoin:** An anticonvulsant that is used in a wide variety of seizures. It is also an anti-arrhythmic and a muscle relaxant. The mechanism of therapeutic action is not clear, although several cellular actions have been described including effects on ion channels, active transport, and general membrane stabilization. The mechanism of its muscle relaxant effect appears to involve a reduction in the sensitivity of muscle spindles to stretch. Phenytoin has been proposed for several other therapeutic uses, but its use has been limited by its many adverse effects and interactions with other drugs. [NIH]

**Phorbol:** Class of chemicals that promotes the development of tumors. [NIH]

**Phorbol Esters:** Tumor-promoting compounds obtained from croton oil (Croton tiglium). Some of these are used in cell biological experiments as activators of protein kinase C. [NIH]

**Phosphodiesterase:** Effector enzyme that regulates the levels of a second messenger, the cyclic GMP. [NIH]

**Phospholipases:** A class of enzymes that catalyze the hydrolysis of phosphoglycerides or glycerophosphatidates. EC 3.1.-. [NIH]

**Phospholipids:** Lipids containing one or more phosphate groups, particularly those derived from either glycerol (phosphoglycerides; glycerophospholipids) or sphingosine (sphingolipids). They are polar lipids that are of great importance for the structure and function of cell membranes and are the most abundant of membrane lipids, although not stored in large amounts in the system. [NIH]

**Phosphorus:** A non-metallic element that is found in the blood, muscles, nevers, bones, and teeth, and is a component of adenosine triphosphate (ATP; the primary energy source for the body's cells.) [NIH]

**Phosphorylase:** An enzyme of the transferase class that catalyzes the phosphorylysis of a terminal alpha-1,4-glycosidic bond at the non-reducing end of a glycogen molecule, releasing a glucose 1-phosphate residue. Phosphorylase should be qualified by the natural substance acted upon. EC 2.4.1.1. [NIH]

**Phosphorylated:** Attached to a phosphate group. [NIH]

**Phosphorylates:** Attached to a phosphate group. [NIH]

**Phosphorylation:** The introduction of a phosphoryl group into a compound through the formation of an ester bond between the compound and a phosphorus moiety. [NIH]

**Phototransduction:** The transducing of light energy to afferent nerve impulses, such as takes place in the retinal rods and cones. After light photons are absorbed by the photopigments, the signal is transmitted to the outer segment membrane by the cyclic GMP second messenger system, where it closes the sodium channels. This channel gating ultimately generates an action potential in the inner retina. [NIH]

**Phylogeny:** The relationships of groups of organisms as reflected by their evolutionary history. [NIH]

**Physical Examination:** Systematic and thorough inspection of the patient for physical signs

of disease or abnormality. [NIH]

**Physical Fitness:** A state of well-being in which performance is optimal, often as a result of physical conditioning which may be prescribed for disease therapy. [NIH]

**Physical Therapy:** The restoration of function and the prevention of disability following disease or injury with the use of light, heat, cold, water, electricity, ultrasound, and exercise. [NIH]

**Physiologic:** Having to do with the functions of the body. When used in the phrase "physiologic age," it refers to an age assigned by general health, as opposed to calendar age. [NIH]

**Physiology:** The science that deals with the life processes and functions of organismus, their cells, tissues, and organs. [NIH]

**Phytic Acid:** Complexing agent for removal of traces of heavy metal ions. It acts also as a hypocalcemic agent. [NIH]

**Pigments:** Any normal or abnormal coloring matter in plants, animals, or micro-organisms. [NIH]

**Piloerection:** Involuntary erection or bristling of hairs. [NIH]

**Pilot study:** The initial study examining a new method or treatment. [NIH]

**Plants:** Multicellular, eukaryotic life forms of the kingdom Plantae. They are characterized by a mainly photosynthetic mode of nutrition; essentially unlimited growth at localized regions of cell divisions (meristems); cellulose within cells providing rigidity; the absence of organs of locomotion; absense of nervous and sensory systems; and an alteration of haploid and diploid generations. [NIH]

**Plasma:** The clear, yellowish, fluid part of the blood that carries the blood cells. The proteins that form blood clots are in plasma. [NIH]

**Plasma cells:** A type of white blood cell that produces antibodies. [NIH]

**Plasmapheresis:** Procedure whereby plasma is separated and extracted from anticoagulated whole blood and the red cells retransfused to the donor. Plasmapheresis is also employed for therapeutic use. [NIH]

**Plastids:** Self-replicating cytoplasmic organelles of plant and algal cells that contain pigments and may synthesize and accumulate various substances. Plastids are used in phylogenetic studies. [NIH]

**Platelet Activation:** A series of progressive, overlapping events triggered by exposure of the platelets to subendothelial tissue. These events include shape change, adhesiveness, aggregation, and release reactions. When carried through to completion, these events lead to the formation of a stable hemostatic plug. [NIH]

**Platelet Aggregation:** The attachment of platelets to one another. This clumping together can be induced by a number of agents (e.g., thrombin, collagen) and is part of the mechanism leading to the formation of a thrombus. [NIH]

**Platelets:** A type of blood cell that helps prevent bleeding by causing blood clots to form. Also called thrombocytes. [NIH]

**Platinum:** Platinum. A heavy, soft, whitish metal, resembling tin, atomic number 78, atomic weight 195.09, symbol Pt. (From Dorland, 28th ed) It is used in manufacturing equipment for laboratory and industrial use. It occurs as a black powder (platinum black) and as a spongy substance (spongy platinum) and may have been known in Pliny's time as "alutiae". [NIH]

**Plexus:** A network or tangle; a general term for a network of lymphatic vessels, nerves, or veins. [EU]

**Pneumoconiosis:** Condition characterized by permanent deposition of substantial amounts of particulate matter in the lungs, usually of occupational or environmental origin, and by the tissue reaction to its presence. [NIH]

**Pneumonia:** Inflammation of the lungs. [NIH]

**Podophyllotoxin:** The main active constituent of the resin from the roots of may apple or mandrake (Podophyllum peltatum and P. emodi). It is a potent spindle poison, toxic if taken internally, and has been used as a cathartic. It is very irritating to skin and mucous membranes, has keratolytic actions, has been used to treat warts and keratoses, and may have antineoplastic properties, as do some of its congeners and derivatives. [NIH]

**Point Mutation:** A mutation caused by the substitution of one nucleotide for another. This results in the DNA molecule having a change in a single base pair. [NIH]

**Poisoning:** A condition or physical state produced by the ingestion, injection or inhalation of, or exposure to a deleterious agent. [NIH]

**Poliomyelitis:** An acute viral disease, occurring sporadically and in epidemics, and characterized clinically by fever, sore throat, headache, and vomiting, often with stiffness of the neck and back. In the minor illness these may be the only symptoms. The major illness, which may or may not be preceded by the minor illness, is characterized by involvement of the central nervous system, stiff neck, pleocytosis in the spinal fluid, and perhaps paralysis. There may be subsequent atrophy of groups of muscles, ending in contraction and permanent deformity. The major illness is called acute anterior p., infantile paralysis and Heine-Medin disease. The disease is now largely controlled by vaccines. [EU]

**Polyarthritis:** An inflammation of several joints together. [EU]

**Polycystic:** An inherited disorder characterized by many grape-like clusters of fluid-filled cysts that make both kidneys larger over time. These cysts take over and destroy working kidney tissue. PKD may cause chronic renal failure and end-stage renal disease. [NIH]

**Polycythemia Vera:** A myeloproliferative disorder of unknown etiology, characterized by abnormal proliferation of all hematopoietic bone marrow elements and an absolute increase in red cell mass and total blood volume, associated frequently with splenomegaly, leukocytosis, and thrombocythemia. Hematopoiesis is also reactive in extramedullary sites (liver and spleen). In time myelofibrosis occurs. [NIH]

**Polymers:** Compounds formed by the joining of smaller, usually repeating, units linked by covalent bonds. These compounds often form large macromolecules (e.g., polypeptides, proteins, plastics). [NIH]

**Polymorphic:** Occurring in several or many forms; appearing in different forms at different stages of development. [EU]

**Polymorphism:** The occurrence together of two or more distinct forms in the same population. [NIH]

**Polymyalgia Rheumatica:** A syndrome in the elderly characterized by proximal joint and muscle pain, high erythrocyte sedimentation rate, and a self-limiting course. Pain is usually accompanied by evidence of an inflammatory reaction. Women are affected twice as commonly as men and Caucasians more frequently than other groups. The condition is frequently associated with temporal arteritis and some theories pose the possibility that the two diseases arise from a single etiology or even that they are the same entity. [NIH]

**Polyneuropathies:** Diseases of multiple peripheral nerves. The various forms are categorized by the type of nerve affected (e.g., sensory, motor, or autonomic), by the distribution of nerve injury (e.g., distal vs. proximal), by nerve component primarily affected (e.g., demyelinating vs. axonal), by etiology, or by pattern of inheritance. [NIH]

**Polysaccharide:** A type of carbohydrate. It contains sugar molecules that are linked together chemically. [NIH]

**Polyuria:** Urination of a large volume of urine with an increase in urinary frequency, commonly seen in diabetes. [NIH]

**Porphyria:** A group of disorders characterized by the excessive production of porphyrins or their precursors that arises from abnormalities in the regulation of the porphyrin-heme pathway. The porphyrias are usually divided into three broad groups, erythropoietic, hepatic, and erythrohepatic, according to the major sites of abnormal porphyrin synthesis. [NIH]

**Porphyrins:** A group of compounds containing the porphin structure, four pyrrole rings connected by methine bridges in a cyclic configuration to which a variety of side chains are attached. The nature of the side chain is indicated by a prefix, as uroporphyrin, hematoporphyrin, etc. The porphyrins, in combination with iron, form the heme component in biologically significant compounds such as hemoglobin and myoglobin. [NIH]

**Posterior:** Situated in back of, or in the back part of, or affecting the back or dorsal surface of the body. In lower animals, it refers to the caudal end of the body. [EU]

**Postherpetic Neuralgia:** Variety of neuralgia associated with migraine in which pain is felt in or behind the eye. [NIH]

**Postnatal:** Occurring after birth, with reference to the newborn. [EU]

**Postoperative:** After surgery. [NIH]

**Postsynaptic:** Nerve potential generated by an inhibitory hyperpolarizing stimulation. [NIH]

**Post-translational:** The cleavage of signal sequence that directs the passage of the protein through a cell or organelle membrane. [NIH]

**Post-traumatic:** Occurring as a result of or after injury. [EU]

**Postural:** Pertaining to posture or position. [EU]

**Potassium:** An element that is in the alkali group of metals. It has an atomic symbol K, atomic number 19, and atomic weight 39.10. It is the chief cation in the intracellular fluid of muscle and other cells. Potassium ion is a strong electrolyte and it plays a significant role in the regulation of fluid volume and maintenance of the water-electrolyte balance. [NIH]

**Potassium Channels:** Cell membrane glycoproteins selective for potassium ions. [NIH]

**Potentiates:** A degree of synergism which causes the exposure of the organism to a harmful substance to worsen a disease already contracted. [NIH]

**Potentiating:** A degree of synergism which causes the exposure of the organism to a harmful substance to worsen a disease already contracted. [NIH]

**Potentiation:** An overall effect of two drugs taken together which is greater than the sum of the effects of each drug taken alone. [NIH]

**Practice Guidelines:** Directions or principles presenting current or future rules of policy for the health care practitioner to assist him in patient care decisions regarding diagnosis, therapy, or related clinical circumstances. The guidelines may be developed by government agencies at any level, institutions, professional societies, governing boards, or by the convening of expert panels. The guidelines form a basis for the evaluation of all aspects of health care and delivery. [NIH]

**Preclinical:** Before a disease becomes clinically recognizable. [EU]

**Precursor:** Something that precedes. In biological processes, a substance from which another, usually more active or mature substance is formed. In clinical medicine, a sign or symptom that heralds another. [EU]

**Predisposition:** A latent susceptibility to disease which may be activated under certain conditions, as by stress. [EU]

**Prednisolone:** A glucocorticoid with the general properties of the corticosteroids. It is the drug of choice for all conditions in which routine systemic corticosteroid therapy is indicated, except adrenal deficiency states. [NIH]

**Prescription Fees:** The charge levied on the consumer for drugs or therapy prescribed under written order of a physician or other health professional. [NIH]

**Presynaptic:** Situated proximal to a synapse, or occurring before the synapse is crossed. [EU]

**Prevalence:** The total number of cases of a given disease in a specified population at a designated time. It is differentiated from incidence, which refers to the number of new cases in the population at a given time. [NIH]

**Prickle:** Several layers of the epidermis where the individual cells are connected by cell bridges. [NIH]

**Prion:** Small proteinaceous infectious particles that resist inactivation by procedures modifying nucleic acids and contain an abnormal isoform of a cellular protein which is a major and necessary component. [NIH]

**Progeny:** The offspring produced in any generation. [NIH]

**Progeria:** An abnormal congenital condition characterized by premature aging in children, where all the changes of cell senescence occur. It is manifested by premature greying, hair loss, hearing loss, cataracts, arthritis,osteoporosis, diabetes mellitus, atrophy of subcutaneous fat, skeletal hypoplasia, and accelerated atherosclerosis. Many affected individuals develop malignant tumors, especially sarcomas. [NIH]

**Progesterone:** Pregn-4-ene-3,20-dione. The principal progestational hormone of the body, secreted by the corpus luteum, adrenal cortex, and placenta. Its chief function is to prepare the uterus for the reception and development of the fertilized ovum. It acts as an antiovulatory agent when administered on days 5-25 of the menstrual cycle. [NIH]

**Progression:** Increase in the size of a tumor or spread of cancer in the body. [NIH]

**Progressive:** Advancing; going forward; going from bad to worse; increasing in scope or severity. [EU]

**Projection:** A defense mechanism, operating unconsciously, whereby that which is emotionally unacceptable in the self is rejected and attributed (projected) to others. [NIH]

**Proline:** A non-essential amino acid that is synthesized from glutamic acid. It is an essential component of collagen and is important for proper functioning of joints and tendons. [NIH]

**Promoter:** A chemical substance that increases the activity of a carcinogenic process. [NIH]

**Prone:** Having the front portion of the body downwards. [NIH]

**Pro-Opiomelanocortin:** A precursor protein, MW 30,000, synthesized mainly in the anterior pituitary gland but also found in the hypothalamus, brain, and several peripheral tissues. It incorporates the amino acid sequences of ACTH and beta-lipotropin. These two hormones, in turn, contain the biologically active peptides MSH, corticotropin-like intermediate lobe peptide, alpha-lipotropin, endorphins, and methionine enkephalin. [NIH]

**Prophase:** The first phase of cell division, in which the chromosomes become visible, the nucleus starts to lose its identity, the spindle appears, and the centrioles migrate toward opposite poles. [NIH]

**Proportional:** Being in proportion : corresponding in size, degree, or intensity, having the same or a constant ratio; of, relating to, or used in determining proportions. [EU]

**Prospective study:** An epidemiologic study in which a group of individuals (a cohort), all

free of a particular disease and varying in their exposure to a possible risk factor, is followed over a specific amount of time to determine the incidence rates of the disease in the exposed and unexposed groups. [NIH]

**Prostate:** A gland in males that surrounds the neck of the bladder and the urethra. It secretes a substance that liquifies coagulated semen. It is situated in the pelvic cavity behind the lower part of the pubic symphysis, above the deep layer of the triangular ligament, and rests upon the rectum. [NIH]

**Prostatectomy:** Complete or partial surgical removal of the prostate. Three primary approaches are commonly employed: suprapubic - removal through an incision above the pubis and through the urinary bladder; retropubic - as for suprapubic but without entering the urinary bladder; and transurethral (transurethral resection of prostate). [NIH]

**Protease:** Proteinase (= any enzyme that catalyses the splitting of interior peptide bonds in a protein). [EU]

**Protease Inhibitors:** Compounds which inhibit or antagonize biosynthesis or actions of proteases (endopeptidases). [NIH]

**Protective Agents:** Synthetic or natural substances which are given to prevent a disease or disorder or are used in the process of treating a disease or injury due to a poisonous agent. [NIH]

**Protein Binding:** The process in which substances, either endogenous or exogenous, bind to proteins, peptides, enzymes, protein precursors, or allied compounds. Specific protein-binding measures are often used as assays in diagnostic assessments. [NIH]

**Protein C:** A vitamin-K dependent zymogen present in the blood, which, upon activation by thrombin and thrombomodulin exerts anticoagulant properties by inactivating factors Va and VIIIa at the rate-limiting steps of thrombin formation. [NIH]

**Protein Kinase C:** An enzyme that phosphorylates proteins on serine or threonine residues in the presence of physiological concentrations of calcium and membrane phospholipids. The additional presence of diacylglycerols markedly increases its sensitivity to both calcium and phospholipids. The sensitivity of the enzyme can also be increased by phorbol esters and it is believed that protein kinase C is the receptor protein of tumor-promoting phorbol esters. EC 2.7.1.-. [NIH]

**Protein S:** The vitamin K-dependent cofactor of activated protein C. Together with protein C, it inhibits the action of factors VIIIa and Va. A deficiency in protein S can lead to recurrent venous and arterial thrombosis. [NIH]

**Proteins:** Polymers of amino acids linked by peptide bonds. The specific sequence of amino acids determines the shape and function of the protein. [NIH]

**Proteinuria:** The presence of protein in the urine, indicating that the kidneys are not working properly. [NIH]

**Proteolytic:** 1. Pertaining to, characterized by, or promoting proteolysis. 2. An enzyme that promotes proteolysis (= the splitting of proteins by hydrolysis of the peptide bonds with formation of smaller polypeptides). [EU]

**Prothrombin:** A plasma protein that is the inactive precursor of thrombin. It is converted to thrombin by a prothrombin activator complex consisting of factor Xa, factor V, phospholipid, and calcium ions. Deficiency of prothrombin leads to hypoprothrombinemia. [NIH]

**Protocol:** The detailed plan for a clinical trial that states the trial's rationale, purpose, drug or vaccine dosages, length of study, routes of administration, who may participate, and other aspects of trial design. [NIH]

**Protons:** Stable elementary particles having the smallest known positive charge, found in the nuclei of all elements. The proton mass is less than that of a neutron. A proton is the nucleus of the light hydrogen atom, i.e., the hydrogen ion. [NIH]

**Proto-Oncogene Proteins:** Products of proto-oncogenes. Normally they do not have oncogenic or transforming properties, but are involved in the regulation or differentiation of cell growth. They often have protein kinase activity. [NIH]

**Proto-Oncogene Proteins c-mos:** Cellular proteins encoded by the c-mos genes. They function in the cell cycle to maintain maturation promoting factor in the active state and have protein-serine/threonine kinase activity. Oncogenic transformation can take place when c-mos proteins are expressed at the wrong time. [NIH]

**Protozoa:** A subkingdom consisting of unicellular organisms that are the simplest in the animal kingdom. Most are free living. They range in size from submicroscopic to macroscopic. Protozoa are divided into seven phyla: Sarcomastigophora, Labyrinthomorpha, Apicomplexa, Microspora, Ascetospora, Myxozoa, and Ciliophora. [NIH]

**Proximal:** Nearest; closer to any point of reference; opposed to distal. [EU]

**Pruritic:** Pertaining to or characterized by pruritus. [EU]

**Pseudotumor Cerebri:** A condition marked by raised intracranial pressure and characterized clinically by headaches; nausea; papilledema, peripheral constriction of the visual fields, transient visual obscurations, and pulsatile tinnitus. Obesity is frequently associated with this condition, which primarily affects women between 20 and 44 years of age. Chronic papilledema may lead to optic nerve injury (optic nerve diseases) and visual loss (blindness). [NIH]

**Psoriasis:** A common genetically determined, chronic, inflammatory skin disease characterized by rounded erythematous, dry, scaling patches. The lesions have a predilection for nails, scalp, genitalia, extensor surfaces, and the lumbosacral region. Accelerated epidermopoiesis is considered to be the fundamental pathologic feature in psoriasis. [NIH]

**Psychic:** Pertaining to the psyche or to the mind; mental. [EU]

**Psychomotor:** Pertaining to motor effects of cerebral or psychic activity. [EU]

**Psychosis:** A mental disorder characterized by gross impairment in reality testing as evidenced by delusions, hallucinations, markedly incoherent speech, or disorganized and agitated behaviour without apparent awareness on the part of the patient of the incomprehensibility of his behaviour; the term is also used in a more general sense to refer to mental disorders in which mental functioning is sufficiently impaired as to interfere grossly with the patient's capacity to meet the ordinary demands of life. Historically, the term has been applied to many conditions, e.g. manic-depressive psychosis, that were first described in psychotic patients, although many patients with the disorder are not judged psychotic. [EU]

**Ptosis:** 1. Prolapse of an organ or part. 2. Drooping of the upper eyelid from paralysis of the third nerve or from sympathetic innervation. [EU]

**Public Health:** Branch of medicine concerned with the prevention and control of disease and disability, and the promotion of physical and mental health of the population on the international, national, state, or municipal level. [NIH]

**Public Policy:** A course or method of action selected, usually by a government, from among alternatives to guide and determine present and future decisions. [NIH]

**Pulmonary:** Relating to the lungs. [NIH]

**Pulmonary Artery:** The short wide vessel arising from the conus arteriosus of the right

ventricle and conveying unaerated blood to the lungs. [NIH]

**Pulmonary Edema:** An accumulation of an excessive amount of watery fluid in the lungs, may be caused by acute exposure to dangerous concentrations of irritant gasses. [NIH]

**Pulse:** The rhythmical expansion and contraction of an artery produced by waves of pressure caused by the ejection of blood from the left ventricle of the heart as it contracts. [NIH]

**Pupil:** The aperture in the iris through which light passes. [NIH]

**Purines:** A series of heterocyclic compounds that are variously substituted in nature and are known also as purine bases. They include adenine and guanine, constituents of nucleic acids, as well as many alkaloids such as caffeine and theophylline. Uric acid is the metabolic end product of purine metabolism. [NIH]

**Purpura:** Purplish or brownish red discoloration, easily visible through the epidermis, caused by hemorrhage into the tissues. [NIH]

**Purulent:** Consisting of or containing pus; associated with the formation of or caused by pus. [EU]

**Pyoderma:** Any purulent skin disease (Dorland, 27th ed). [NIH]

**Pyogenic:** Producing pus; pyopoietic (= liquid inflammation product made up of cells and a thin fluid called liquor puris). [EU]

**Pyrimidines:** A family of 6-membered heterocyclic compounds occurring in nature in a wide variety of forms. They include several nucleic acid constituents (cytosine, thymine, and uracil) and form the basic structure of the barbiturates. [NIH]

**Quality of Life:** A generic concept reflecting concern with the modification and enhancement of life attributes, e.g., physical, political, moral and social environment. [NIH]

**Race:** A population within a species which exhibits general similarities within itself, but is both discontinuous and distinct from other populations of that species, though not sufficiently so as to achieve the status of a taxon. [NIH]

**Racemic:** Optically inactive but resolvable in the way of all racemic compounds. [NIH]

**Radiation:** Emission or propagation of electromagnetic energy (waves/rays), or the waves/rays themselves; a stream of electromagnetic particles (electrons, neutrons, protons, alpha particles) or a mixture of these. The most common source is the sun. [NIH]

**Radiation therapy:** The use of high-energy radiation from x-rays, gamma rays, neutrons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body in the area near cancer cells (internal radiation therapy, implant radiation, or brachytherapy). Systemic radiation therapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that circulates throughout the body. Also called radiotherapy. [NIH]

**Radioactive:** Giving off radiation. [NIH]

**Radiography:** Examination of any part of the body for diagnostic purposes by means of roentgen rays, recording the image on a sensitized surface (such as photographic film). [NIH]

**Radiological:** Pertaining to radiodiagnostic and radiotherapeutic procedures, and interventional radiology or other planning and guiding medical radiology. [NIH]

**Radiology:** A specialty concerned with the use of x-ray and other forms of radiant energy in the diagnosis and treatment of disease. [NIH]

**Radius:** The lateral bone of the forearm. [NIH]

**Randomized:** Describes an experiment or clinical trial in which animal or human subjects are assigned by chance to separate groups that compare different treatments. [NIH]

**Reagent:** A substance employed to produce a chemical reaction so as to detect, measure, produce, etc., other substances. [EU]

**Reality Testing:** The individual's objective evaluation of the external world and the ability to differentiate adequately between it and the internal world; considered to be a primary ego function. [NIH]

**Receptor:** A molecule inside or on the surface of a cell that binds to a specific substance and causes a specific physiologic effect in the cell. [NIH]

**Receptors, Serotonin:** Cell-surface proteins that bind serotonin and trigger intracellular changes which influence the behavior of cells. Several types of serotonin receptors have been recognized which differ in their pharmacology, molecular biology, and mode of action. [NIH]

**Recombinant:** A cell or an individual with a new combination of genes not found together in either parent; usually applied to linked genes. [EU]

**Recombinant Proteins:** Proteins prepared by recombinant DNA technology. [NIH]

**Recombination:** The formation of new combinations of genes as a result of segregation in crosses between genetically different parents; also the rearrangement of linked genes due to crossing-over. [NIH]

**Rectum:** The last 8 to 10 inches of the large intestine. [NIH]

**Recurrence:** The return of a sign, symptom, or disease after a remission. [NIH]

**Red Nucleus:** A pinkish-yellow portion of the midbrain situated in the rostral mesencephalic tegmentum. It receives a large projection from the contralateral half of the cerebellum via the superior cerebellar peduncle and a projection from the ipsilateral motor cortex. [NIH]

**Reductase:** Enzyme converting testosterone to dihydrotestosterone. [NIH]

**Refer:** To send or direct for treatment, aid, information, de decision. [NIH]

**Reflex:** An involuntary movement or exercise of function in a part, excited in response to a stimulus applied to the periphery and transmitted to the brain or spinal cord. [NIH]

**Refraction:** A test to determine the best eyeglasses or contact lenses to correct a refractive error (myopia, hyperopia, or astigmatism). [NIH]

**Refractive Power:** The ability of an object, such as the eye, to bend light as light passes through it. [NIH]

**Refractory:** Not readily yielding to treatment. [EU]

**Regeneration:** The natural renewal of a structure, as of a lost tissue or part. [EU]

**Regimen:** A treatment plan that specifies the dosage, the schedule, and the duration of treatment. [NIH]

**Relapse:** The return of signs and symptoms of cancer after a period of improvement. [NIH]

**Remission:** A decrease in or disappearance of signs and symptoms of cancer. In partial remission, some, but not all, signs and symptoms of cancer have disappeared. In complete remission, all signs and symptoms of cancer have disappeared, although there still may be cancer in the body. [NIH]

**Respiration:** The act of breathing with the lungs, consisting of inspiration, or the taking into the lungs of the ambient air, and of expiration, or the expelling of the modified air which contains more carbon dioxide than the air taken in (Blakiston's Gould Medical Dictionary, 4th ed.). This does not include tissue respiration (= oxygen consumption) or cell respiration

(= cell respiration). [NIH]

**Restless legs:** Legs characterized by or showing inability to remain at rest. [EU]

**Restoration:** Broad term applied to any inlay, crown, bridge or complete denture which restores or replaces loss of teeth or oral tissues. [NIH]

**Reticular:** Coarse-fibered, netlike dermis layer. [NIH]

**Retina:** The ten-layered nervous tissue membrane of the eye. It is continuous with the optic nerve and receives images of external objects and transmits visual impulses to the brain. Its outer surface is in contact with the choroid and the inner surface with the vitreous body. The outer-most layer is pigmented, whereas the inner nine layers are transparent. [NIH]

**Retinal:** 1. Pertaining to the retina. 2. The aldehyde of retinol, derived by the oxidative enzymatic splitting of absorbed dietary carotene, and having vitamin A activity. In the retina, retinal combines with opsins to form visual pigments. One isomer, 11-cis retinal combines with opsin in the rods (scotopsin) to form rhodopsin, or visual purple. Another, all-trans retinal (trans-r.); visual yellow; xanthopsin) results from the bleaching of rhodopsin by light, in which the 11-cis form is converted to the all-trans form. Retinal also combines with opsins in the cones (photopsins) to form the three pigments responsible for colour vision. Called also retinal, and retinene1. [EU]

**Retinal Ganglion Cells:** Cells of the innermost nuclear layer of the retina, the ganglion cell layer, which project axons through the optic nerve to the brain. They are quite variable in size and in the shapes of their dendritic arbors, which are generally confined to the inner plexiform layer. [NIH]

**Retinoblastoma:** An eye cancer that most often occurs in children younger than 5 years. It occurs in hereditary and nonhereditary (sporadic) forms. [NIH]

**Retinol:** Vitamin A. It is essential for proper vision and healthy skin and mucous membranes. Retinol is being studied for cancer prevention; it belongs to the family of drugs called retinoids. [NIH]

**Retinopathy:** 1. Retinitis (= inflammation of the retina). 2. Retinosis (= degenerative, noninflammatory condition of the retina). [EU]

**Retrobulbar:** Behind the pons. [EU]

**Retrograde:** 1. Moving backward or against the usual direction of flow. 2. Degenerating, deteriorating, or catabolic. [EU]

**Retropubic:** A potential space between the urinary bladder and the symphisis and body of the pubis. [NIH]

**Retrospective:** Looking back at events that have already taken place. [NIH]

**Retroviral vector:** RNA from a virus that is used to insert genetic material into cells. [NIH]

**Retrovirus:** A member of a group of RNA viruses, the RNA of which is copied during viral replication into DNA by reverse transcriptase. The viral DNA is then able to be integrated into the host chromosomal DNA. [NIH]

**Rheology:** The study of the deformation and flow of matter, usually liquids or fluids, and of the plastic flow of solids. The concept covers consistency, dilatancy, liquefaction, resistance to flow, shearing, thixotrophy, and viscosity. [NIH]

**Rheumatic Diseases:** Disorders of connective tissue, especially the joints and related structures, characterized by inflammation, degeneration, or metabolic derangement. [NIH]

**Rheumatism:** A group of disorders marked by inflammation or pain in the connective tissue structures of the body. These structures include bone, cartilage, and fat. [NIH]

**Rheumatoid:** Resembling rheumatism. [EU]

**Rheumatoid arthritis:** A form of arthritis, the cause of which is unknown, although infection, hypersensitivity, hormone imbalance and psychologic stress have been suggested as possible causes. [NIH]

**Rhinitis:** Inflammation of the mucous membrane of the nose. [NIH]

**Rhodopsin:** A photoreceptor protein found in retinal rods. It is a complex formed by the binding of retinal, the oxidized form of retinol, to the protein opsin and undergoes a series of complex reactions in response to visible light resulting in the transmission of nerve impulses to the brain. [NIH]

**Ribonucleoside Diphosphate Reductase:** An enzyme of the oxidoreductase class that catalyzes the formation of 2'-deoxyribonucleotides from the corresponding ribonucleotides using NADPH as the ultimate electron donor. The deoxyribonucleoside diphosphates are used in DNA synthesis. (From Dorland, 27th ed) EC 1.17.4.1. [NIH]

**Ribose:** A pentose active in biological systems usually in its D-form. [NIH]

**Ribosome:** A granule of protein and RNA, synthesized in the nucleolus and found in the cytoplasm of cells. Ribosomes are the main sites of protein synthesis. Messenger RNA attaches to them and there receives molecules of transfer RNA bearing amino acids. [NIH]

**Rickets:** A condition caused by deficiency of vitamin D, especially in infancy and childhood, with disturbance of normal ossification. The disease is marked by bending and distortion of the bones under muscular action, by the formation of nodular enlargements on the ends and sides of the bones, by delayed closure of the fontanelles, pain in the muscles, and sweating of the head. Vitamin D and sunlight together with an adequate diet are curative, provided that the parathyroid glands are functioning properly. [EU]

**Rigidity:** Stiffness or inflexibility, chiefly that which is abnormal or morbid; rigor. [EU]

**Risk factor:** A habit, trait, condition, or genetic alteration that increases a person's chance of developing a disease. [NIH]

**Risk patient:** Patient who is at risk, because of his/her behaviour or because of the type of person he/she is. [EU]

**Ritonavir:** An HIV protease inhibitor that works by interfering with the reproductive cycle of HIV. [NIH]

**Rod:** A reception for vision, located in the retina. [NIH]

**Rodenticides:** Substances used to destroy or inhibit the action of rats, mice, or other rodents. [NIH]

**Salivary:** The duct that convey saliva to the mouth. [NIH]

**Salivary glands:** Glands in the mouth that produce saliva. [NIH]

**Saponins:** Sapogenin glycosides. A type of glycoside widely distributed in plants. Each consists of a sapogenin as the aglycon moiety, and a sugar. The sapogenin may be a steroid or a triterpene and the sugar may be glucose, galactose, a pentose, or a methylpentose. Sapogenins are poisonous towards the lower forms of life and are powerful hemolytics when injected into the blood stream able to dissolve red blood cells at even extreme dilutions. [NIH]

**Sarcoid:** A cutaneus lesion occurring as a manifestation of sarcoidosis. [NIH]

**Sarcoidosis:** An idiopathic systemic inflammatory granulomatous disorder comprised of epithelioid and multinucleated giant cells with little necrosis. It usually invades the lungs with fibrosis and may also involve lymph nodes, skin, liver, spleen, eyes, phalangeal bones, and parotid glands. [NIH]

**Sarcoma:** A connective tissue neoplasm formed by proliferation of mesodermal cells; it is

usually highly malignant. [NIH]

**Schizophrenia:** A mental disorder characterized by a special type of disintegration of the personality. [NIH]

**Schwann:** A neurilemmal cell from the sheath of a peripheral nerve fiber. [NIH]

**Schwann Cells:** Neuroglial cells of the peripheral nervous system which form the insulating myelin sheaths of peripheral axons. [NIH]

**Sciatic Nerve:** A nerve which originates in the lumbar and sacral spinal cord (L4 to S3) and supplies motor and sensory innervation to the lower extremity. The sciatic nerve, which is the main continuation of the sacral plexus, is the largest nerve in the body. It has two major branches, the tibial nerve and the peroneal nerve. [NIH]

**Scleroderma:** A chronic disorder marked by hardening and thickening of the skin. Scleroderma can be localized or it can affect the entire body (systemic). [NIH]

**Sclerosis:** A pathological process consisting of hardening or fibrosis of an anatomical structure, often a vessel or a nerve. [NIH]

**Screening:** Checking for disease when there are no symptoms. [NIH]

**Second Messenger Systems:** Systems in which an intracellular signal is generated in response to an intercellular primary messenger such as a hormone or neurotransmitter. They are intermediate signals in cellular processes such as metabolism, secretion, contraction, phototransduction, and cell growth. Examples of second messenger systems are the adenyl cyclase-cyclic AMP system, the phosphatidylinositol diphosphate-inositol triphosphate system, and the cyclic GMP system. [NIH]

**Secretion:** 1. The process of elaborating a specific product as a result of the activity of a gland; this activity may range from separating a specific substance of the blood to the elaboration of a new chemical substance. 2. Any substance produced by secretion. [EU]

**Sedative:** 1. Allaying activity and excitement. 2. An agent that allays excitement. [EU]

**Sedimentation:** The act of causing the deposit of sediment, especially by the use of a centrifugal machine. [EU]

**Segregation:** The separation in meiotic cell division of homologous chromosome pairs and their contained allelomorphic gene pairs. [NIH]

**Seizures:** Clinical or subclinical disturbances of cortical function due to a sudden, abnormal, excessive, and disorganized discharge of brain cells. Clinical manifestations include abnormal motor, sensory and psychic phenomena. Recurrent seizures are usually referred to as epilepsy or "seizure disorder." [NIH]

**Selective estrogen receptor modulator:** SERM. A drug that acts like estrogen on some tissues, but blocks the effect of estrogen on other tissues. Tamoxifen and raloxifene are SERMs. [NIH]

**Selegiline:** A selective, irreversible inhibitor of Type B monoamine oxidase. It is used in newly diagnosed patients with Parkinson's disease. It may slow progression of the clinical disease and delay the requirement for levodopa therapy. It also may be given with levodopa upon onset of disability. (From AMA Drug Evaluations Annual, 1994, p385) The compound without isomeric designation is Deprenyl. [NIH]

**Selenium:** An element with the atomic symbol Se, atomic number 34, and atomic weight 78.96. It is an essential micronutrient for mammals and other animals but is toxic in large amounts. Selenium protects intracellular structures against oxidative damage. It is an essential component of glutathione peroxidase. [NIH]

**Self Care:** Performance of activities or tasks traditionally performed by professional health

care providers. The concept includes care of oneself or one's family and friends. [NIH]

**Semen:** The thick, yellowish-white, viscid fluid secretion of male reproductive organs discharged upon ejaculation. In addition to reproductive organ secretions, it contains spermatozoa and their nutrient plasma. [NIH]

**Semisynthetic:** Produced by chemical manipulation of naturally occurring substances. [EU]

**Senescence:** The bodily and mental state associated with advancing age. [NIH]

**Senile:** Relating or belonging to old age; characteristic of old age; resulting from infirmity of old age. [NIH]

**Sensibility:** The ability to receive, feel and appreciate sensations and impressions; the quality of being sensitive; the extend to which a method gives results that are free from false negatives. [NIH]

**Sensor:** A device designed to respond to physical stimuli such as temperature, light, magnetism or movement and transmit resulting impulses for interpretation, recording, movement, or operating control. [NIH]

**Sensory loss:** A disease of the nerves whereby the myelin or insulating sheath of myelin on the nerves does not stay intact and the messages from the brain to the muscles through the nerves are not carried properly. [NIH]

**Sensory Thresholds:** The minimum amount of stimulus energy necessary to elicit a sensory response. [NIH]

**Sequence Analysis:** A multistage process that includes the determination of a sequence (protein, carbohydrate, etc.), its fragmentation and analysis, and the interpretation of the resulting sequence information. [NIH]

**Sequencing:** The determination of the order of nucleotides in a DNA or RNA chain. [NIH]

**Serine:** A non-essential amino acid occurring in natural form as the L-isomer. It is synthesized from glycine or threonine. It is involved in the biosynthesis of purines, pyrimidines, and other amino acids. [NIH]

**Serotonin:** A biochemical messenger and regulator, synthesized from the essential amino acid L-tryptophan. In humans it is found primarily in the central nervous system, gastrointestinal tract, and blood platelets. Serotonin mediates several important physiological functions including neurotransmission, gastrointestinal motility, hemostasis, and cardiovascular integrity. Multiple receptor families (receptors, serotonin) explain the broad physiological actions and distribution of this biochemical mediator. [NIH]

**Serum:** The clear liquid part of the blood that remains after blood cells and clotting proteins have been removed. [NIH]

**Sex Characteristics:** Those characteristics that distinguish one sex from the other. The primary sex characteristics are the ovaries and testes and their related hormones. Secondary sex characteristics are those which are masculine or feminine but not directly related to reproduction. [NIH]

**Sex Determination:** The biological characteristics which distinguish human beings as female or male. [NIH]

**Shock:** The general bodily disturbance following a severe injury; an emotional or moral upset occasioned by some disturbing or unexpected experience; disruption of the circulation, which can upset all body functions: sometimes referred to as circulatory shock. [NIH]

**Sibutramine:** A drug used for the management of obesity that helps reduce food intake and is indicated for weight loss and maintenance of weight loss when used in conjunction with a

reduced-calorie diet. It works to suppress the appetite primarily by inhibiting the reuptake of the neurotransmitters norepinephrine and serotonin. Side effects include dry mouth, headache, constipation, insomnia, and a slight increase in average blood pressure. In some patients it causes a higher blood pressure increase. [NIH]

**Sicca:** Failure of lacrimal secretion, keratoconjunctivitis sicca, failure of secretion of the salivary glands and mucous glands of the upper respiratory tract and polyarthritis. [NIH]

**Side effect:** A consequence other than the one(s) for which an agent or measure is used, as the adverse effects produced by a drug, especially on a tissue or organ system other than the one sought to be benefited by its administration. [EU]

**Signal Transduction:** The intercellular or intracellular transfer of information (biological activation/inhibition) through a signal pathway. In each signal transduction system, an activation/inhibition signal from a biologically active molecule (hormone, neurotransmitter) is mediated via the coupling of a receptor/enzyme to a second messenger system or to an ion channel. Signal transduction plays an important role in activating cellular functions, cell differentiation, and cell proliferation. Examples of signal transduction systems are the GABA-postsynaptic receptor-calcium ion channel system, the receptor-mediated T-cell activation pathway, and the receptor-mediated activation of phospholipases. Those coupled to membrane depolarization or intracellular release of calcium include the receptor-mediated activation of cytotoxic functions in granulocytes and the synaptic potentiation of protein kinase activation. Some signal transduction pathways may be part of larger signal transduction pathways; for example, protein kinase activation is part of the platelet activation signal pathway. [NIH]

**Signs and Symptoms:** Clinical manifestations that can be either objective when observed by a physician, or subjective when perceived by the patient. [NIH]

**Silicosis:** A type of pneumoconiosis caused by inhalation of particles of silica, quartz, ganister or slate. [NIH]

**Skeletal:** Having to do with the skeleton (boney part of the body). [NIH]

**Skeleton:** The framework that supports the soft tissues of vertebrate animals and protects many of their internal organs. The skeletons of vertebrates are made of bone and/or cartilage. [NIH]

**Skull:** The skeleton of the head including the bones of the face and the bones enclosing the brain. [NIH]

**Small intestine:** The part of the digestive tract that is located between the stomach and the large intestine. [NIH]

**Smooth muscle:** Muscle that performs automatic tasks, such as constricting blood vessels. [NIH]

**Social Environment:** The aggregate of social and cultural institutions, forms, patterns, and processes that influence the life of an individual or community. [NIH]

**Sodium:** An element that is a member of the alkali group of metals. It has the atomic symbol Na, atomic number 11, and atomic weight 23. With a valence of 1, it has a strong affinity for oxygen and other nonmetallic elements. Sodium provides the chief cation of the extracellular body fluids. Its salts are the most widely used in medicine. (From Dorland, 27th ed) Physiologically the sodium ion plays a major role in blood pressure regulation, maintenance of fluid volume, and electrolyte balance. [NIH]

**Sodium Channels:** Cell membrane glycoproteins selective for sodium ions. Fast sodium current is associated with the action potential in neural membranes. [NIH]

**Soft tissue:** Refers to muscle, fat, fibrous tissue, blood vessels, or other supporting tissue of

the body. [NIH]

**Solid tumor:** Cancer of body tissues other than blood, bone marrow, or the lymphatic system. [NIH]

**Solitary Nucleus:** Gray matter located in the dorsomedial part of the medulla oblongata associated with the solitary tract. The solitary nucleus receives inputs from most organ systems including the terminations of the facial, glossopharyngeal, and vagus nerves. It is a major coordinator of autonomic nervous system regulation of cardiovascular, respiratory, gustatory, gastrointestinal, and chemoreceptive aspects of homeostasis. The solitary nucleus is also notable for the large number of neurotransmitters which are found therein. [NIH]

**Solvent:** 1. Dissolving; effecting a solution. 2. A liquid that dissolves or that is capable of dissolving; the component of a solution that is present in greater amount. [EU]

**Soma:** The body as distinct from the mind; all the body tissue except the germ cells; all the axial body. [NIH]

**Somatic:** 1. Pertaining to or characteristic of the soma or body. 2. Pertaining to the body wall in contrast to the viscera. [EU]

**Sorbitol:** A polyhydric alcohol with about half the sweetness of sucrose. Sorbitol occurs naturally and is also produced synthetically from glucose. It was formerly used as a diuretic and may still be used as a laxative and in irrigating solutions for some surgical procedures. It is also used in many manufacturing processes, as a pharmaceutical aid, and in several research applications. [NIH]

**Sound wave:** An alteration of properties of an elastic medium, such as pressure, particle displacement, or density, that propagates through the medium, or a superposition of such alterations. [NIH]

**Spasm:** An involuntary contraction of a muscle or group of muscles. Spasms may involve skeletal muscle or smooth muscle. [NIH]

**Spastic:** 1. Of the nature of or characterized by spasms. 2. Hypertonic, so that the muscles are stiff and the movements awkward. 3. A person exhibiting spasticity, such as occurs in spastic paralysis or in cerebral palsy. [EU]

**Spasticity:** A state of hypertonicity, or increase over the normal tone of a muscle, with heightened deep tendon reflexes. [EU]

**Spatial disorientation:** Loss of orientation in space where person does not know which way is up. [NIH]

**Specialist:** In medicine, one who concentrates on 1 special branch of medical science. [NIH]

**Species:** A taxonomic category subordinate to a genus (or subgenus) and superior to a subspecies or variety, composed of individuals possessing common characters distinguishing them from other categories of individuals of the same taxonomic level. In taxonomic nomenclature, species are designated by the genus name followed by a Latin or Latinized adjective or noun. [EU]

**Specificity:** Degree of selectivity shown by an antibody with respect to the number and types of antigens with which the antibody combines, as well as with respect to the rates and the extents of these reactions. [NIH]

**Spectrum:** A charted band of wavelengths of electromagnetic vibrations obtained by refraction and diffraction. By extension, a measurable range of activity, such as the range of bacteria affected by an antibiotic (antibacterial s.) or the complete range of manifestations of a disease. [EU]

**Sperm:** The fecundating fluid of the male. [NIH]

**Spices:** The dried seeds, bark, root, stems, buds, leaves, or fruit of aromatic plants used to season food. [NIH]

**Spinal cord:** The main trunk or bundle of nerves running down the spine through holes in the spinal bone (the vertebrae) from the brain to the level of the lower back. [NIH]

**Spinal Cord Diseases:** Pathologic conditions which feature spinal cord damage or dysfunction, including disorders involving the meninges and perimeningeal spaces surrounding the spinal cord. Traumatic injuries, vascular diseases, infections, and inflammatory/autoimmune processes may affect the spinal cord. [NIH]

**Spinal Cord Vascular Diseases:** Hypoxic-ischemic and hemorrhagic disorders of the spinal cord. Arteriosclerosis, emboli, and vascular malformations are potential causes of these conditions. [NIH]

**Spinal Nerves:** The 31 paired peripheral nerves formed by the union of the dorsal and ventral spinal roots from each spinal cord segment. The spinal nerve plexuses and the spinal roots are also included. [NIH]

**Spinous:** Like a spine or thorn in shape; having spines. [NIH]

**Spirochete:** Lyme disease. [NIH]

**Spleen:** An organ that is part of the lymphatic system. The spleen produces lymphocytes, filters the blood, stores blood cells, and destroys old blood cells. It is located on the left side of the abdomen near the stomach. [NIH]

**Splenomegaly:** Enlargement of the spleen. [NIH]

**Spondylitis:** Inflammation of the vertebrae. [EU]

**Sporadic:** Neither endemic nor epidemic; occurring occasionally in a random or isolated manner. [EU]

**Sprains and Strains:** A collective term for muscle and ligament injuries without dislocation or fracture. A sprain is a joint injury in which some of the fibers of a supporting ligament are ruptured but the continuity of the ligament remains intact. A strain is an overstretching or overexertion of some part of the musculature. [NIH]

**Stabilization:** The creation of a stable state. [EU]

**Staging:** Performing exams and tests to learn the extent of the cancer within the body, especially whether the disease has spread from the original site to other parts of the body. [NIH]

**Standard therapy:** A currently accepted and widely used treatment for a certain type of cancer, based on the results of past research. [NIH]

**Standardize:** To compare with or conform to a standard; to establish standards. [EU]

**Stavudine:** A dideoxynucleoside analog that inhibits reverse transcriptase and has in vitro activity against HIV. [NIH]

**Steel:** A tough, malleable, iron-based alloy containing up to, but no more than, two percent carbon and often other metals. It is used in medicine and dentistry in implants and instrumentation. [NIH]

**Stem cell transplantation:** A method of replacing immature blood-forming cells that were destroyed by cancer treatment. The stem cells are given to the person after treatment to help the bone marrow recover and continue producing healthy blood cells. [NIH]

**Stem Cells:** Relatively undifferentiated cells of the same lineage (family type) that retain the ability to divide and cycle throughout postnatal life to provide cells that can become specialized and take the place of those that die or are lost. [NIH]

**Steroid:** A group name for lipids that contain a hydrogenated cyclopentanoperhydrophenanthrene ring system. Some of the substances included in this group are progesterone, adrenocortical hormones, the gonadal hormones, cardiac aglycones, bile acids, sterols (such as cholesterol), toad poisons, saponins, and some of the carcinogenic hydrocarbons. [EU]

**Steroid therapy:** Treatment with corticosteroid drugs to reduce swelling, pain, and other symptoms of inflammation. [NIH]

**Stimulant:** 1. Producing stimulation; especially producing stimulation by causing tension on muscle fibre through the nervous tissue. 2. An agent or remedy that produces stimulation. [EU]

**Stimulus:** That which can elicit or evoke action (response) in a muscle, nerve, gland or other excitable issue, or cause an augmenting action upon any function or metabolic process. [NIH]

**Stomach:** An organ of digestion situated in the left upper quadrant of the abdomen between the termination of the esophagus and the beginning of the duodenum. [NIH]

**Stool:** The waste matter discharged in a bowel movement; feces. [NIH]

**Stress:** Forcibly exerted influence; pressure. Any condition or situation that causes strain or tension. Stress may be either physical or psychologic, or both. [NIH]

**Stroke:** Sudden loss of function of part of the brain because of loss of blood flow. Stroke may be caused by a clot (thrombosis) or rupture (hemorrhage) of a blood vessel to the brain. [NIH]

**Stupor:** Partial or nearly complete unconsciousness, manifested by the subject's responding only to vigorous stimulation. Also, in psychiatry, a disorder marked by reduced responsiveness. [EU]

**Subacute:** Somewhat acute; between acute and chronic. [EU]

**Subarachnoid:** Situated or occurring between the arachnoid and the pia mater. [EU]

**Subclinical:** Without clinical manifestations; said of the early stage(s) of an infection or other disease or abnormality before symptoms and signs become apparent or detectable by clinical examination or laboratory tests, or of a very mild form of an infection or other disease or abnormality. [EU]

**Subcutaneous:** Beneath the skin. [NIH]

**Subspecies:** A category intermediate in rank between species and variety, based on a smaller number of correlated characters than are used to differentiate species and generally conditioned by geographical and/or ecological occurrence. [NIH]

**Substance P:** An eleven-amino acid neurotransmitter that appears in both the central and peripheral nervous systems. It is involved in transmission of pain, causes rapid contractions of the gastrointestinal smooth muscle, and modulates inflammatory and immune responses. [NIH]

**Substrate:** A substance upon which an enzyme acts. [EU]

**Substrate Specificity:** A characteristic feature of enzyme activity in relation to the kind of substrate on which the enzyme or catalytic molecule reacts. [NIH]

**Sulfur:** An element that is a member of the chalcogen family. It has an atomic symbol S, atomic number 16, and atomic weight 32.066. It is found in the amino acids cysteine and methionine. [NIH]

**Supplementation:** Adding nutrients to the diet. [NIH]

**Support group:** A group of people with similar disease who meet to discuss how better to cope with their cancer and treatment. [NIH]

**Suppression:** A conscious exclusion of disapproved desire contrary with repression, in

which the process of exclusion is not conscious. [NIH]

**Sural Nerve:** A branch of the tibial nerve which supplies sensory innervation to parts of the lower leg and foot. [NIH]

**Suramin:** A polyanionic compound with an unknown mechanism of action. It is used parenterally in the treatment of African trypanosomiasis and it has been used clinically with diethylcarbamazine to kill the adult Onchocerca. (From AMA Drug Evaluations Annual, 1992, p1643) It has also been shown to have potent antineoplastic properties. [NIH]

**Surface Plasmon Resonance:** A biosensing technique in which biomolecules capable of binding to specific analytes or ligands are first immobilized on one side of a metallic film. Light is then focused on the opposite side of the film to excite the surface plasmons, that is, the oscillations of free electrons propagating along the film's surface. The refractive index of light reflecting off this surface is measured. When the immobilized biomolecules are bound by their ligands, an alteration in surface plasmons on the opposite side of the film is created which is directly proportional to the change in bound, or adsorbed, mass. Binding is measured by changes in the refractive index. The technique is used to study biomolecular interactions, such as antigen-antibody binding. [NIH]

**Sweat:** The fluid excreted by the sweat glands. It consists of water containing sodium chloride, phosphate, urea, ammonia, and other waste products. [NIH]

**Sympathetic Nervous System:** The thoracolumbar division of the autonomic nervous system. Sympathetic preganglionic fibers originate in neurons of the intermediolateral column of the spinal cord and project to the paravertebral and prevertebral ganglia, which in turn project to target organs. The sympathetic nervous system mediates the body's response to stressful situations, i.e., the fight or flight reactions. It often acts reciprocally to the parasympathetic system. [NIH]

**Sympathomimetic:** 1. Mimicking the effects of impulses conveyed by adrenergic postganglionic fibres of the sympathetic nervous system. 2. An agent that produces effects similar to those of impulses conveyed by adrenergic postganglionic fibres of the sympathetic nervous system. Called also adrenergic. [EU]

**Symphysis:** A secondary cartilaginous joint. [NIH]

**Symptomatic:** Having to do with symptoms, which are signs of a condition or disease. [NIH]

**Symptomatic treatment:** Therapy that eases symptoms without addressing the cause of disease. [NIH]

**Synapse:** The region where the processes of two neurons come into close contiguity, and the nervous impulse passes from one to the other; the fibers of the two are intermeshed, but, according to the general view, there is no direct contiguity. [NIH]

**Synaptic:** Pertaining to or affecting a synapse (= site of functional apposition between neurons, at which an impulse is transmitted from one neuron to another by electrical or chemical means); pertaining to synapsis (= pairing off in point-for-point association of homologous chromosomes from the male and female pronuclei during the early prophase of meiosis). [EU]

**Synaptic Transmission:** The communication from a neuron to a target (neuron, muscle, or secretory cell) across a synapse. In chemical synaptic transmission, the presynaptic neuron releases a neurotransmitter that diffuses across the synaptic cleft and binds to specific synaptic receptors. These activated receptors modulate ion channels and/or second-messenger systems to influence the postsynaptic cell. Electrical transmission is less common in the nervous system, and, as in other tissues, is mediated by gap junctions. [NIH]

**Synchrony:** The normal physiologic sequencing of atrial and ventricular activation and

contraction. [NIH]

**Systemic:** Affecting the entire body. [NIH]

**Systemic disease:** Disease that affects the whole body. [NIH]

**Systemic lupus erythematosus:** SLE. A chronic inflammatory connective tissue disease marked by skin rashes, joint pain and swelling, inflammation of the kidneys, inflammation of the fibrous tissue surrounding the heart (i.e., the pericardium), as well as other problems. Not all affected individuals display all of these problems. May be referred to as lupus. [NIH]

**Systolic:** Indicating the maximum arterial pressure during contraction of the left ventricle of the heart. [EU]

**Tamoxifen:** A first generation selective estrogen receptor modulator (SERM). It acts as an agonist for bone tissue and cholesterol metabolism but is an estrogen antagonist in mammary and uterine. [NIH]

**Tardive:** Marked by lateness, late; said of a disease in which the characteristic lesion is late in appearing. [EU]

**Taurine:** 2-Aminoethanesulfonic acid. A conditionally essential nutrient, important during mammalian development. It is present in milk but is isolated mostly from ox bile and strongly conjugates bile acids. [NIH]

**Taxanes:** Anticancer drugs that inhibit cancer cell growth by stopping cell division. Also called antimitotic or antimicrotubule agents or mitotic inhibitors. [NIH]

**Telangiectasia:** The permanent enlargement of blood vessels, causing redness in the skin or mucous membranes. [NIH]

**Temporal:** One of the two irregular bones forming part of the lateral surfaces and base of the skull, and containing the organs of hearing. [NIH]

**Tendon:** A discrete band of connective tissue mainly composed of parallel bundles of collagenous fibers by which muscles are attached, or two muscles bellies joined. [NIH]

**Teniposide:** A semisynthetic derivative of podophyllotoxin that exhibits antitumor activity. Teniposide inhibits DNA synthesis by forming a complex with topoisomerase II and DNA. This complex induces breaks in double stranded DNA and prevents repair by topoisomerase II binding. Accumulated breaks in DNA prevent cells from entering into the mitotic phase of the cell cycle, and lead to cell death. Teniposide acts primarily in the G2 and S phases of the cycle. [NIH]

**Tenosynovitis:** Inflammation of a tendon sheath. [EU]

**Teratogenic:** Tending to produce anomalies of formation, or teratism (= anomaly of formation or development : condition of a monster). [EU]

**Terminator:** A DNA sequence sited at the end of a transcriptional unit that signals the end of transcription. [NIH]

**Testosterone:** A hormone that promotes the development and maintenance of male sex characteristics. [NIH]

**Tetrahydrocannabinol:** A psychoactive compound extracted from the resin of Cannabis sativa (marihuana, hashish). The isomer delta-9-tetrahydrocannabinol (THC) is considered the most active form, producing characteristic mood and perceptual changes associated with this compound. Dronabinol is a synthetic form of delta-9-THC. [NIH]

**Thalamic:** Cell that reaches the lateral nucleus of amygdala. [NIH]

**Thalamic Diseases:** Disorders of the centrally located thalamus, which integrates a wide range of cortical and subcortical information. Manifestations include sensory loss, movement disorders; ataxia, pain syndromes, visual disorders, a variety of

neuropsychological conditions, and coma. Relatively common etiologies include cerebrovascular disorders; craniocerebral trauma; brain neoplasms; brain hypoxia; intracranial hemorrhages; and infectious processes. [NIH]

**Therapeutics:** The branch of medicine which is concerned with the treatment of diseases, palliative or curative. [NIH]

**Thermal:** Pertaining to or characterized by heat. [EU]

**Thiamine:** 3-((4-Amino-2-methyl-5-pyrimidinyl)methyl)-5-(2-hydroxyethyl)-4-methylthiazolium chloride. [NIH]

**Thioctic Acid:** A vitamin-like antioxidant that acts as a free-radical scavenger. [NIH]

**Thioguanine:** An antineoplastic compound which also has antimetabolite action. The drug is used in the therapy of acute leukemia. [NIH]

**Thoracic:** Having to do with the chest. [NIH]

**Threonine:** An essential amino acid occurring naturally in the L-form, which is the active form. It is found in eggs, milk, gelatin, and other proteins. [NIH]

**Threshold:** For a specified sensory modality (e. g. light, sound, vibration), the lowest level (absolute threshold) or smallest difference (difference threshold, difference limen) or intensity of the stimulus discernible in prescribed conditions of stimulation. [NIH]

**Thrombin:** An enzyme formed from prothrombin that converts fibrinogen to fibrin. (Dorland, 27th ed) EC 3.4.21.5. [NIH]

**Thrombomodulin:** A cell surface glycoprotein of endothelial cells that binds thrombin and serves as a cofactor in the activation of protein C and its regulation of blood coagulation. [NIH]

**Thrombosis:** The formation or presence of a blood clot inside a blood vessel. [NIH]

**Thymidine:** A chemical compound found in DNA. Also used as treatment for mucositis. [NIH]

**Thymidine Phosphorylase:** The enzyme catalyzing the transfer of 2-deoxy-D-ribose from thymidine to orthophosphate, thereby liberating thymidine. EC 2.4.2.4. [NIH]

**Thyroid:** A gland located near the windpipe (trachea) that produces thyroid hormone, which helps regulate growth and metabolism. [NIH]

**Thyrotropin:** A peptide hormone secreted by the anterior pituitary. It promotes the growth of the thyroid gland and stimulates the synthesis of thyroid hormones and the release of thyroxine by the thyroid gland. [NIH]

**Thyroxine:** An amino acid of the thyroid gland which exerts a stimulating effect on thyroid metabolism. [NIH]

**Tibial Nerve:** The medial terminal branch of the sciatic nerve. The tibial nerve fibers originate in lumbar and sacral spinal segments (L4 to S2). They supply motor and sensory innervation to parts of the calf and foot. [NIH]

**Ticks:** Blood-sucking arachnids of the order Acarina. [NIH]

**Tin:** A trace element that is required in bone formation. It has the atomic symbol Sn, atomic number 50, and atomic weight 118.71. [NIH]

**Tinnitus:** Sounds that are perceived in the absence of any external noise source which may take the form of buzzing, ringing, clicking, pulsations, and other noises. Objective tinnitus refers to noises generated from within the ear or adjacent structures that can be heard by other individuals. The term subjective tinnitus is used when the sound is audible only to the affected individual. Tinnitus may occur as a manifestation of cochlear diseases; vestibulocochlear nerve diseases; intracranial hypertension; craniocerebral trauma; and

other conditions. [NIH]

**Tissue:** A group or layer of cells that are alike in type and work together to perform a specific function. [NIH]

**Tissue Culture:** Maintaining or growing of tissue, organ primordia, or the whole or part of an organ in vitro so as to preserve its architecture and/or function (Dorland, 28th ed). Tissue culture includes both organ culture and cell culture. [NIH]

**Tissue Distribution:** Accumulation of a drug or chemical substance in various organs (including those not relevant to its pharmacologic or therapeutic action). This distribution depends on the blood flow or perfusion rate of the organ, the ability of the drug to penetrate organ membranes, tissue specificity, protein binding. The distribution is usually expressed as tissue to plasma ratios. [NIH]

**Titre:** The quantity of a substance required to produce a reaction with a given volume of another substance, or the amount of one substance required to correspond with a given amount of another substance. [EU]

**Tolerance:** 1. The ability to endure unusually large doses of a drug or toxin. 2. Acquired drug tolerance; a decreasing response to repeated constant doses of a drug or the need for increasing doses to maintain a constant response. [EU]

**Tomography:** Imaging methods that result in sharp images of objects located on a chosen plane and blurred images located above or below the plane. [NIH]

**Tone:** 1. The normal degree of vigour and tension; in muscle, the resistance to passive elongation or stretch; tonus. 2. A particular quality of sound or of voice. 3. To make permanent, or to change, the colour of silver stain by chemical treatment, usually with a heavy metal. [EU]

**Tonicity:** The normal state of muscular tension. [NIH]

**Tonus:** A state of slight tension usually present in muscles even when they are not undergoing active contraction. [NIH]

**Topical:** On the surface of the body. [NIH]

**Toxic:** Having to do with poison or something harmful to the body. Toxic substances usually cause unwanted side effects. [NIH]

**Toxicity:** The quality of being poisonous, especially the degree of virulence of a toxic microbe or of a poison. [EU]

**Toxicology:** The science concerned with the detection, chemical composition, and pharmacologic action of toxic substances or poisons and the treatment and prevention of toxic manifestations. [NIH]

**Toxin:** A poison; frequently used to refer specifically to a protein produced by some higher plants, certain animals, and pathogenic bacteria, which is highly toxic for other living organisms. Such substances are differentiated from the simple chemical poisons and the vegetable alkaloids by their high molecular weight and antigenicity. [EU]

**Trace element:** Substance or element essential to plant or animal life, but present in extremely small amounts. [NIH]

**Trachea:** The cartilaginous and membranous tube descending from the larynx and branching into the right and left main bronchi. [NIH]

**Traction:** The act of pulling. [NIH]

**Transcriptase:** An enzyme which catalyses the synthesis of a complementary mRNA molecule from a DNA template in the presence of a mixture of the four ribonucleotides (ATP, UTP, GTP and CTP). [NIH]

**Transcutaneous:** Transdermal. [EU]

**Transdermal:** Entering through the dermis, or skin, as in administration of a drug applied to the skin in ointment or patch form. [EU]

**Transduction:** The transfer of genes from one cell to another by means of a viral (in the case of bacteria, a bacteriophage) vector or a vector which is similar to a virus particle (pseudovirion). [NIH]

**Transfection:** The uptake of naked or purified DNA into cells, usually eukaryotic. It is analogous to bacterial transformation. [NIH]

**Transferases:** Transferases are enzymes transferring a group, for example, the methyl group or a glycosyl group, from one compound (generally regarded as donor) to another compound (generally regarded as acceptor). The classification is based on the scheme "donor:acceptor group transferase". (Enzyme Nomenclature, 1992) EC 2. [NIH]

**Translation:** The process whereby the genetic information present in the linear sequence of ribonucleotides in mRNA is converted into a corresponding sequence of amino acids in a protein. It occurs on the ribosome and is unidirectional. [NIH]

**Translational:** The cleavage of signal sequence that directs the passage of the protein through a cell or organelle membrane. [NIH]

**Transmitter:** A chemical substance which effects the passage of nerve impulses from one cell to the other at the synapse. [NIH]

**Transplantation:** Transference of a tissue or organ, alive or dead, within an individual, between individuals of the same species, or between individuals of different species. [NIH]

**Transurethral:** Performed through the urethra. [EU]

**Transurethral resection:** Surgery performed with a special instrument inserted through the urethra. Also called TUR. [NIH]

**Transurethral Resection of Prostate:** Resection of the prostate using a cystoscope passed through the urethra. [NIH]

**Trauma:** Any injury, wound, or shock, must frequently physical or structural shock, producing a disturbance. [NIH]

**Tremor:** Cyclical movement of a body part that can represent either a physiologic process or a manifestation of disease. Intention or action tremor, a common manifestation of cerebellar diseases, is aggravated by movement. In contrast, resting tremor is maximal when there is no attempt at voluntary movement, and occurs as a relatively frequent manifestation of Parkinson disease. [NIH]

**Trichomoniasis:** An infection with the protozoan parasite Trichomonas vaginalis. [NIH]

**Tricyclic:** Containing three fused rings or closed chains in the molecular structure. [EU]

**Triglyceride:** A lipid carried through the blood stream to tissues. Most of the body's fat tissue is in the form of triglycerides, stored for use as energy. Triglycerides are obtained primarily from fat in foods. [NIH]

**Truncal:** The bilateral dissection of the abdominal branches of the vagus nerve. [NIH]

**Trypanosomiasis:** Infection with protozoa of the genus Trypanosoma. [NIH]

**Tryptophan:** An essential amino acid that is necessary for normal growth in infants and for nitrogen balance in adults. It is a precursor serotonin and niacin. [NIH]

**Tuberculostatic:** Inhibiting the growth of Mycobacterium tuberculosis. [EU]

**Tuberous Sclerosis:** A rare congenital disease in which the essential pathology is the appearance of multiple tumors in the cerebrum and in other organs, such as the heart or

kidneys. [NIH]

**Tumor model:** A type of animal model which can be used to study the development and progression of diseases and to test new treatments before they are given to humans. Animals with transplanted human cancers or other tissues are called xenograft models. [NIH]

**Tumour:** 1. Swelling, one of the cardinal signs of inflammations; morbid enlargement. 2. A new growth of tissue in which the multiplication of cells is uncontrolled and progressive; called also neoplasm. [EU]

**Type 2 diabetes:** Usually characterized by a gradual onset with minimal or no symptoms of metabolic disturbance and no requirement for exogenous insulin. The peak age of onset is 50 to 60 years. Obesity and possibly a genetic factor are usually present. [NIH]

**Tyramine:** An indirect sympathomimetic. Tyramine does not directly activate adrenergic receptors, but it can serve as a substrate for adrenergic uptake systems and monoamine oxidase so it prolongs the actions of adrenergic transmitters. It also provokes transmitter release from adrenergic terminals. Tyramine may be a neurotransmitter in some invertebrate nervous systems. [NIH]

**Tyrosine:** A non-essential amino acid. In animals it is synthesized from phenylalanine. It is also the precursor of epinephrine, thyroid hormones, and melanin. [NIH]

**Ubiquitin:** A highly conserved 76 amino acid-protein found in all eukaryotic cells. [NIH]

**Ulcer:** A localized necrotic lesion of the skin or a mucous surface. [NIH]

**Unconscious:** Experience which was once conscious, but was subsequently rejected, as the "personal unconscious". [NIH]

**Uremia:** The illness associated with the buildup of urea in the blood because the kidneys are not working effectively. Symptoms include nausea, vomiting, loss of appetite, weakness, and mental confusion. [NIH]

**Urethra:** The tube through which urine leaves the body. It empties urine from the bladder. [NIH]

**Uric:** A kidney stone that may result from a diet high in animal protein. When the body breaks down this protein, uric acid levels rise and can form stones. [NIH]

**Urinary:** Having to do with urine or the organs of the body that produce and get rid of urine. [NIH]

**Urinate:** To release urine from the bladder to the outside. [NIH]

**Urine:** Fluid containing water and waste products. Urine is made by the kidneys, stored in the bladder, and leaves the body through the urethra. [NIH]

**Uterus:** The small, hollow, pear-shaped organ in a woman's pelvis. This is the organ in which a fetus develops. Also called the womb. [NIH]

**Vaccine:** A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms, such as bacteria or viruses. [NIH]

**Vacuoles:** Any spaces or cavities within a cell. They may function in digestion, storage, secretion, or excretion. [NIH]

**Vagus Nerve:** The 10th cranial nerve. The vagus is a mixed nerve which contains somatic afferents (from skin in back of the ear and the external auditory meatus), visceral afferents (from the pharynx, larynx, thorax, and abdomen), parasympathetic efferents (to the thorax and abdomen), and efferents to striated muscle (of the larynx and pharynx). [NIH]

**Valine:** A branched-chain essential amino acid that has stimulant activity. It promotes muscle growth and tissue repair. It is a precursor in the penicillin biosynthetic pathway. [NIH]

**Vasa Nervorum:** Blood vessels supplying the nerves. [NIH]

**Vascular:** Pertaining to blood vessels or indicative of a copious blood supply. [EU]

**Vascular endothelial growth factor:** VEGF. A substance made by cells that stimulates new blood vessel formation. [NIH]

**Vascular Resistance:** An expression of the resistance offered by the systemic arterioles, and to a lesser extent by the capillaries, to the flow of blood. [NIH]

**Vasculitis:** Inflammation of a blood vessel. [NIH]

**Vasoconstriction:** Narrowing of the blood vessels without anatomic change, for which constriction, pathologic is used. [NIH]

**Vasodilation:** Physiological dilation of the blood vessels without anatomic change. For dilation with anatomic change, dilatation, pathologic or aneurysm (or specific aneurysm) is used. [NIH]

**Vasodilator:** An agent that widens blood vessels. [NIH]

**VE:** The total volume of gas either inspired or expired in one minute. [NIH]

**Vector:** Plasmid or other self-replicating DNA molecule that transfers DNA between cells in nature or in recombinant DNA technology. [NIH]

**Vein:** Vessel-carrying blood from various parts of the body to the heart. [NIH]

**Venous:** Of or pertaining to the veins. [EU]

**Ventricle:** One of the two pumping chambers of the heart. The right ventricle receives oxygen-poor blood from the right atrium and pumps it to the lungs through the pulmonary artery. The left ventricle receives oxygen-rich blood from the left atrium and pumps it to the body through the aorta. [NIH]

**Ventricular:** Pertaining to a ventricle. [EU]

**Venules:** The minute vessels that collect blood from the capillary plexuses and join together to form veins. [NIH]

**Vertebrae:** A bony unit of the segmented spinal column. [NIH]

**Vestibular:** Pertaining to or toward a vestibule. In dental anatomy, used to refer to the tooth surface directed toward the vestibule of the mouth. [EU]

**Vestibulocochlear Nerve:** The 8th cranial nerve. The vestibulocochlear nerve has a cochlear part (cochlear nerve) which is concerned with hearing and a vestibular part (vestibular nerve) which mediates the sense of balance and head position. The fibers of the cochlear nerve originate from neurons of the spiral ganglion and project to the cochlear nuclei (cochlear nucleus). The fibers of the vestibular nerve arise from neurons of Scarpa's ganglion and project to the vestibular nuclei. [NIH]

**Veterinary Medicine:** The medical science concerned with the prevention, diagnosis, and treatment of diseases in animals. [NIH]

**Vinca Alkaloids:** A class of alkaloids from the genus of apocyanaceous woody herbs including periwinkles. They are some of the most useful antineoplastic agents. [NIH]

**Vincristine:** An anticancer drug that belongs to the family of plant drugs called vinca alkaloids. [NIH]

**Vinorelbine:** An anticancer drug that belongs to the family of plant drugs called vinca alkaloids. [NIH]

**Viral:** Pertaining to, caused by, or of the nature of virus. [EU]

**Viral Hepatitis:** Hepatitis caused by a virus. Five different viruses (A, B, C, D, and E) most

commonly cause this form of hepatitis. Other rare viruses may also cause hepatitis. [NIH]

**Virulence:** The degree of pathogenicity within a group or species of microorganisms or viruses as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host. [NIH]

**Virulent:** A virus or bacteriophage capable only of lytic growth, as opposed to temperate phages establishing the lysogenic response. [NIH]

**Virus:** Submicroscopic organism that causes infectious disease. In cancer therapy, some viruses may be made into vaccines that help the body build an immune response to, and kill, tumor cells. [NIH]

**Visceral:** , from viscus a viscus) pertaining to a viscus. [EU]

**Visceral Afferents:** The sensory fibers innervating the viscera. [NIH]

**Visual field:** The entire area that can be seen when the eye is forward, including peripheral vision. [NIH]

**Vitamin A:** A substance used in cancer prevention; it belongs to the family of drugs called retinoids. [NIH]

**Vitamin D:** The vitamin that mediates intestinal calcium absorption, bone calcium metabolism, and probably muscle activity. It usually acts as a hormone precursor, requiring 2 stages of metabolism before reaching actual hormonal form. It is isolated from fish liver oils and used in the treatment and prevention of rickets. [NIH]

**Vitreous:** Glasslike or hyaline; often used alone to designate the vitreous body of the eye (corpus vitreum). [EU]

**Vitro:** Descriptive of an event or enzyme reaction under experimental investigation occurring outside a living organism. Parts of an organism or microorganism are used together with artificial substrates and/or conditions. [NIH]

**Vivo:** Outside of or removed from the body of a living organism. [NIH]

**Volition:** Voluntary activity without external compulsion. [NIH]

**Voltage-gated:** It is opened by the altered charge distribution across the cell membrane. [NIH]

**War:** Hostile conflict between organized groups of people. [NIH]

**Wart:** A raised growth on the surface of the skin or other organ. [NIH]

**Weight Gain:** Increase in body weight over existing weight. [NIH]

**Weight-Bearing:** The physical state of supporting an applied load. This often refers to the weight-bearing bones or joints that support the body's weight, especially those in the spine, hip, knee, and foot. [NIH]

**White blood cell:** A type of cell in the immune system that helps the body fight infection and disease. White blood cells include lymphocytes, granulocytes, macrophages, and others. [NIH]

**Windpipe:** A rigid tube, 10 cm long, extending from the cricoid cartilage to the upper border of the fifth thoracic vertebra. [NIH]

**Wound Healing:** Restoration of integrity to traumatized tissue. [NIH]

**Wound Infection:** Invasion of the site of trauma by pathogenic microorganisms. [NIH]

**Xenograft:** The cells of one species transplanted to another species. [NIH]

**X-ray:** High-energy radiation used in low doses to diagnose diseases and in high doses to treat cancer. [NIH]

**Yeasts:** A general term for single-celled rounded fungi that reproduce by budding. Brewers' and bakers' yeasts are Saccharomyces cerevisiae; therapeutic dried yeast is dried yeast. [NIH]

**Zalcitabine:** A dideoxynucleoside compound in which the 3'-hydroxy group on the sugar moiety has been replaced by a hydrogen. This modification prevents the formation of phosphodiester linkages which are needed for the completion of nucleic acid chains. The compound is a potent inhibitor of HIV replication at low concentrations, acting as a chain-terminator of viral DNA by binding to reverse transcriptase. Its principal toxic side effect is axonal degeneration resulting in peripheral neuropathy. [NIH]

**Zidovudine:** A dideoxynucleoside compound in which the 3'-hydroxy group on the sugar moiety has been replaced by an azido group. This modification prevents the formation of phosphodiester linkages which are needed for the completion of nucleic acid chains. The compound is a potent inhibitor of HIV replication, acting as a chain-terminator of viral DNA during reverse transcription. It improves immunologic function, partially reverses the HIV-induced neurological dysfunction, and improves certain other clinical abnormalities associated with AIDS. Its principal toxic effect is dose-dependent suppression of bone marrow, resulting in anemia and leukopenia. [NIH]

**Zygote:** The fertilized ovum. [NIH]

**Zymogen:** Inactive form of an enzyme which can then be converted to the active form, usually by excision of a polypeptide, e. g. trypsinogen is the zymogen of trypsin. [NIH]

# INDEX

**B**

**D**

## I


9 780597 841590